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(54) Title: TRICYCLIC POLYHYDROXYLIC TYROSINE KINASE INHIBITORS

(57) Abstract

Certain tricyclic polyhydroxylic compounds, and their pharmaceutically-acceptable salts, are inhibitors of tyrosine kinase enzymes, and so are useful for the control of tyrosine kinase dependent diseases (e.g., cancer, atherosclerosis).

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TRICYCLIC POLYHYDROXYLIC TYROSINE KINASE INHIBITORS

This invention relates to tricyclic polyhydroxylic compounds which are tyrosine kinase inhibitors useful for the control of cancer, atherosclerosis and angiogenic-based disorders.

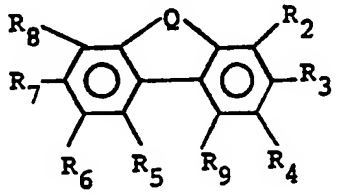
Background of the Invention

Tyrosine-specific protein kinases (tyrosine kinases) represent a family of enzymes which catalyze the transfer of the terminal phosphate of adenosine triphosphate to tyrosine residues in protein substrates. The first members of this class to be identified were tyrosine kinases associated with viral genes (termed oncogenes) which were capable of cell transformation (i.e. pp60v-src and pp98v-fps). Later it was shown that there were normal cellular counterparts (i.e. pp60c-src and pp98c-fps) to these viral gene products. A third category of tyrosine kinases to be identified are those termed the growth factor receptors, which includes insulin, epidermal growth factor, and p185HER-2 receptors. All of these tyrosine kinases are believed, by way of substrate phosphorylation, to play critical roles in signal transduction for a number of cell functions.

Though the exact mechanisms of signal transduction have yet to be elucidated, tyrosine kinases have been shown to be important contributing factors in cell proliferation, carcinogenesis and cell differentiation. Therefore, inhibitors of these tyrosine kinases are useful for the prevention and chemotherapy of proliferative diseases dependent on these enzymes.

Summary of the Invention

This invention is directed to tricyclic polyhydroxylic compounds that are useful as tyrosine kinase inhibitors. The compounds of this invention have the formula



Formula I

and the pharmaceutically-acceptable cationic salts and prodrugs thereof

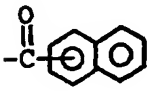
wherein Q is $\diagdown N\text{-}Z_1$, $\diagdown C\text{-}Z_2$ or $-\overset{O}{\overset{\|}{C}}\text{-}X-$;

at least two and no more than four of R_2, R_3, R_4, R_5, R_6, R_7 and R_8 are OH, the remainder being H;

R_9 is H or halo, with the proviso that R_9 is halo only when Q is $\diagdown N\text{-}Z_1$;

Z_1 is H, benzyl, alkyl(C_1-C_4), $-(CH_2)_n$-phenyl-R_{22}, $-(CH_2)_n$-dichlorophenyl,

$-\overset{O}{\overset{\|}{C}}-(CH_2)_n$-phenyl-$R_{20}$, $-SO_2-R_{21}$, $-CH_2$-pyridyl or



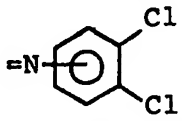
wherein n is 0-3;

R_{20} is H, t-butyl, CF_3, $-SO_2$-alkyl(C_1-C_4), halo, alkyl(C_1-C_4), phenyl or NO_2;

R_{21} is phenyl, alkyl(C_1-C_4), benzyl, nitrophenyl, dichlorophenyl or halophenyl;

R_{22} is $-C\equiv N$, CF_3, phenylsulfonyl, halo or alkyl(C_1-C_4);

Z_2 is H, =O, benzyl, hydroxylbenzyl, =N-phenyl-R_{10} =CH-phenyl-R_{10}, -CH_2-pyridyl, -CH_2-quinolyl, =CH_2-pyridyl, =CH-quinolyl or



wherein R_{10} is -C≡N, H, CF_3, OH, NO_2, alkyl(C_1-C_4) or -SO_2-alkyl(C_1-C_4) with the proviso that when Z_2 is bonded with a single bond to the carbon to which it is attached that that carbon is also bonded to a hydrogen;

X is N-Z_3 or O; and

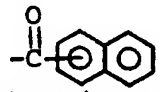
Z_3 is H, alkyl(C_1-C_4), -CH_2phenyl-R_{11} or (dichlorophenyl)methyl wherein R_{11} is H, -NO_2, -SO_2-  , hydroxyl or halo.

A first group of preferred compounds of Formula I are compounds wherein R_2, R_3 and R_4 are H or OH; R_6 and R_7 are OH; R_5 and R_8 are H; R_9 is H or halo;

Q is 

Z_1 is H, benzyl, alkyl(C_1-C_4), -$(CH_2)_n$-phenyl-R_{22}, -$(CH_2)_n$-dichlorophenyl,

 , -SO_2-R_{21}, -CH_2-pyridyl, and

 ;

wherein n is 0-3;

R_{20} is H, t-butyl, CF_3, -SO_2-alkyl(C_1-C_4), halo, alkyl(C_1-C_4), phenyl or NO_2;

R_{21} is phenyl, alkyl(C_1-C_4), benzyl, nitrophenyl, dichlorophenyl or halophenyl; and

R_{22} is -C≡N, CF_3, phenylsulfonyl, halo or alkyl(C_1-C_4).

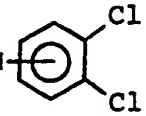
A first group of especially preferred compounds within this first preferred group of Formula I compounds are compounds wherein R_2, R_3, R_6 and R_7 are OH; R_5 and R_8 are H; and R_9 is H or halo. A second group of especially preferred compounds within this first preferred group of Formula I compounds are compounds wherein R_3, R_4, R_6, R_7 are OH; R_2, R_5, R_8 and R_9 are H; and Z_1 is

H, -C(=O)-phenyl, benzyl, -alkyl(C_1-C_4), $-SO_2$-phenyl, $-SO_2$-alkyl(C_1-C_4) and $-CH_2$-3-pyridyl. A third group of especially preferred compounds within this first preferred group of Formula I compounds are compounds wherein R_2, R_3, R_4, R_5, R_8 and R_9 are H; R_6 and R_7 are OH; and

Z_1 is H or  .

A second group of preferred compounds of Formula I are compounds wherein

Q is  ;

Z_2 is H, =O, benzyl, hydroxybenzyl, =N-phenyl-R_{10}, =CH-phenyl-R_{10}, $-CH_2$-pyridyl, $-CH_2$-quinolyl, $=CH_2$-pyridyl, =CH-quinolyl or  ; and

R_{10} is -C≡N, H, CF_3, OH, NO_2, alkyl(C_1-C_4) and $-SO_2$-alkyl(C_1-C_4).

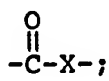
A first group of especially preferred compounds within this second preferred group of Formula I compounds are compounds wherein R_3, R_4, R_6 and R_7 are OH and R_2, R_5, R_8 are H.

A second group of especially preferred compounds within this second group of preferred Formula I compounds are compounds wherein R_3, R_4, R_7 and R_8 are OH and R_2, R_5 and R_6 are H.

A third group of especially preferred compounds within this second preferred group of Formula I compounds are compounds wherein Z_2 is H or =O; R_6 and R_7 are OH; and R_2, R_3, R_4, R_5 and R_8 are H.

A fourth group of especially preferred compounds within this second preferred group of Formula I compounds are compounds wherein Z_2 is =O, benzyl, H, $-CH_2$-4-pyridyl, $-CH_2$-4-quinolyl, =CH-4-pyridyl, =CH-4-quinolyl or =CH-phenyl; R_7 and R_8 are OH; and R_2, R_3, R_4, R_5 and R_6 are H.

A third group of preferred compounds are compounds of formula I wherein Q is



Z_3 is H, alkyl(C_1-C_4), $-CH_2$-phenyl-R_{11} or (dichlorophenyl)methyl; and

R_{11} is H, $-NO_2$, $-SO_2$-  , hydroxyl or halo. A first group of especially preferred compounds within this third preferred group are compounds wherein X is -O-; and R_5 is H. A second group of especially preferred compounds within this third preferred group are compounds wherein X is N-Z_3; R_3, R_4, R_6 and R_7 are OH; and R_2, R_5 and R_8 are H. A third group of especially preferred compounds within this third preferred group are compounds wherein X is N-Z_3; R_3, R_4, R_7 and R_8 are OH; and R_2, R_5 and R_6 are H. A fourth group of especially preferred compounds within this third preferred group are compounds wherein X is N-Z_3; Z_3 and R_5 are H; and any two R_2, R_3, R_4, R_6, R_7 and R_8 are OH.

The present invention is also directed to pharmaceutical compositions for the control of tyrosine kinase dependent diseases in mammals which comprise a compound of the formula I in a pharmaceutically-acceptable carrier; and to a method of controlling tyrosine kinase dependent diseases which comprises administering to a mammal suffering from tyrosine kinase dependent diseases a tyrosine kinase dependent disease controlling amount of a compound of the formula I or ellagic acid.

The expression "pharmaceutically-acceptable cationic salt" refers to nontoxic cationic salts such as (but not limited to) sodium, potassium, calcium, magnesium, ammonium or protonated benzathine (N,N'-dibenzylethylenediamine), choline, ethanolamine, diethanolamine, ethylenediamine, meglamine (N-methyl-glucamine), benethamine (N-benzylphenethylamine), piperazine or tromethamine (2-amino-2-hydroxymethyl-1,3-propanediol).

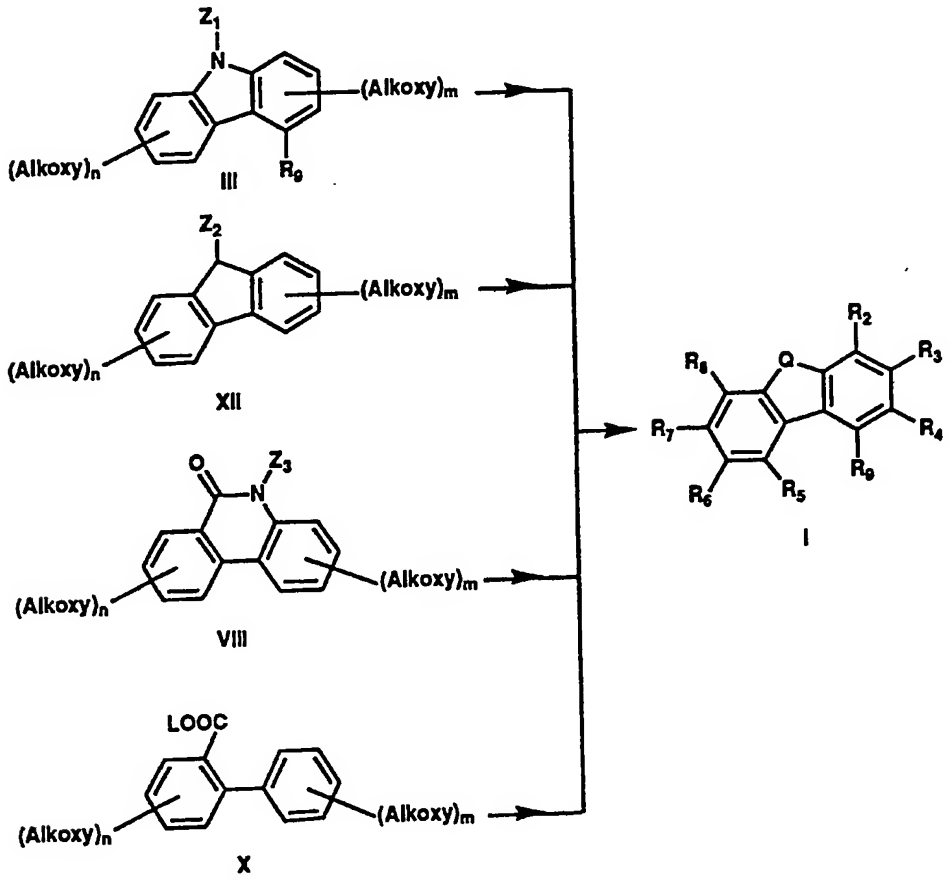
The expression "prodrug" refers to compounds which are drug precursors which, following administration and absorption, release the drug in vivo via some metabolic process. Exemplary prodrugs are alkyl ethers and acyl esters of the phenolic compounds such as methylether, esters of alkanoic (C_1-C_{10})acids, and acids of the formula

wherein n is 1 to 6 and X is an amino or carboxyl (acid, ester) group, and the formula

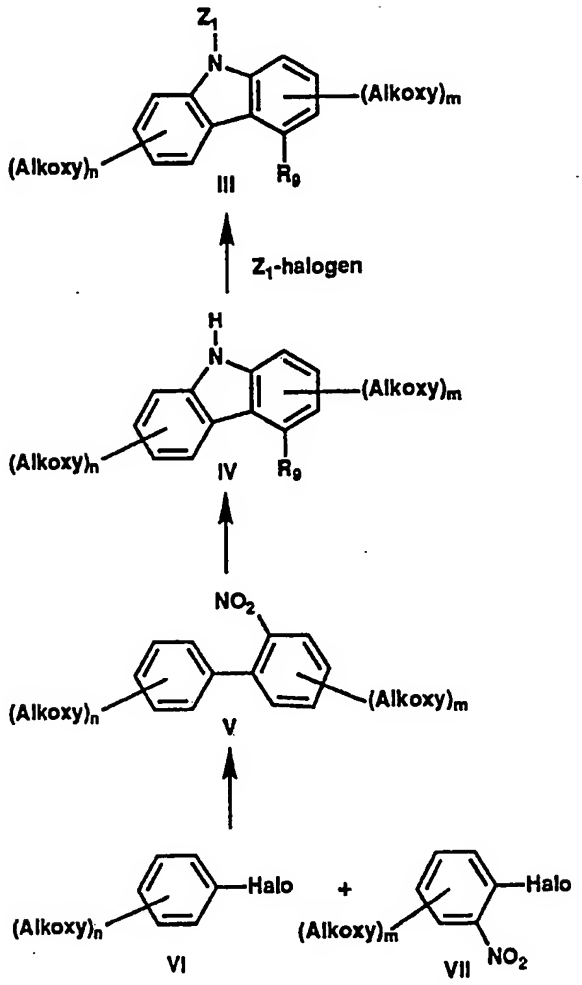
Other features and advantages will be apparent from the specification and claims.

Detailed Description of the Invention

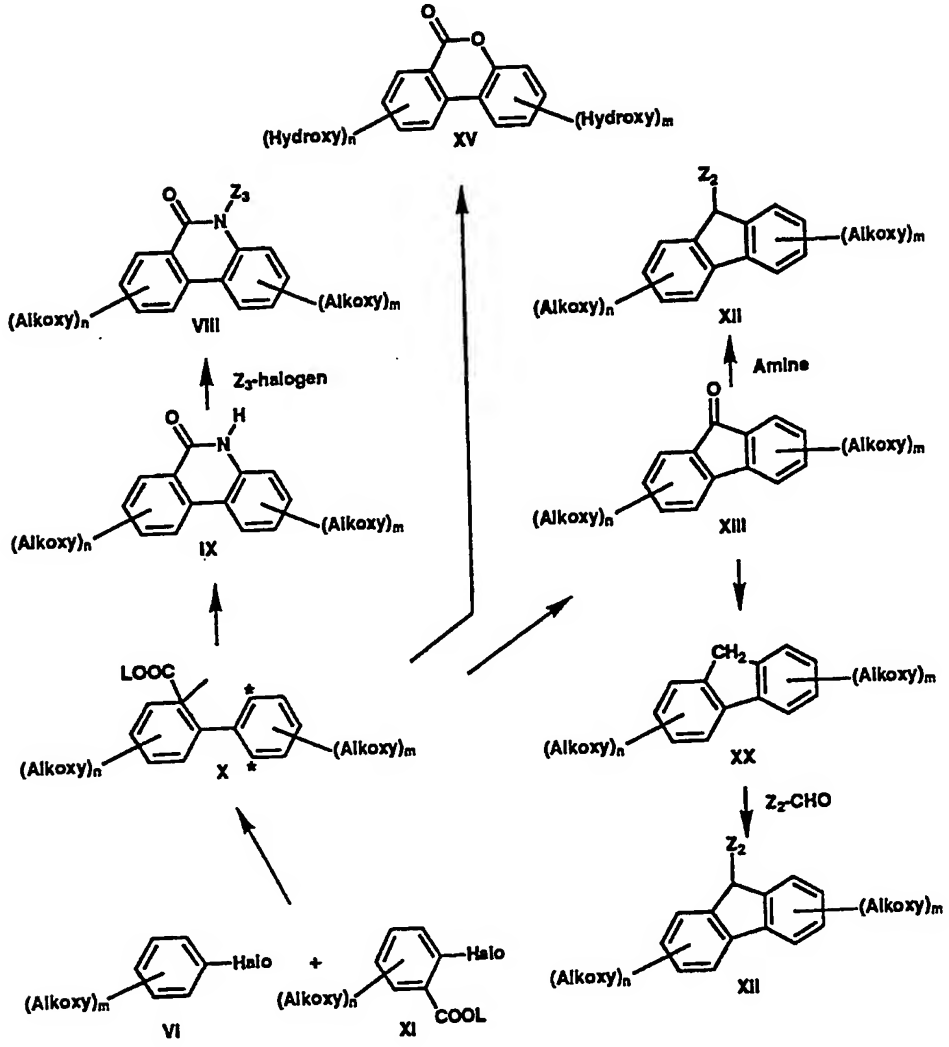
Reaction Scheme I



Reaction Scheme II

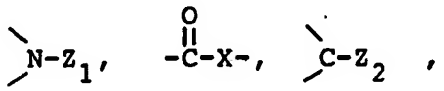


Reaction Scheme III



Ellagic acid is a natural product and is available from Aldrich Co. Its preparation is disclosed in Annual Drug Data Report 1986, 978 and Drugs of the Future 1986, 11, 1029.

According to Reaction Scheme I the desired Formula I compounds wherein Q and R_2-R_9 are as defined above may be prepared by deprotecting the appropriate formula III, XII and VIII compounds wherein



and R_9 are as defined above and n + m is at least two and no more than four. Alkoxy is defined as C_1-C_4.

The deprotection is generally performed in a non-hydroxylic solvent (that is preferably non-coordinating with the below described demethylating agent) preferably a chlorinated solvent such as carbon tetrachloride or methylene chloride. A demethylating agent such as boron tribromide, trialkylsilylhalides, is added to the formula III, XII or VIII compound solution at a temperature of about 0°C to about 80°C for about 1 hour to about 24 hours at pressures of about 0.1 psi to about 50 psi although typically the reaction is conducted at ambient pressures. Alternatively these demethylations can be run in aqueous HBr at a temperature of about 50°C to 100°C using the above pressures and times. Typically, a ratio of about 2 to about 5 equivalents of boron tribromide to the Formula III, XII or VII compound is used. Preferably, the reaction is performed in

dichloromethane with boron tribromide at ambient temperature and pressure for 2 to 24 hours.

In addition, according to Reaction Schemes I and III the desired Formula I compounds wherein Q is

(i.e. Formula XV compounds); X is -O-; and n and m are as defined above; are prepared by deprotection/ cyclization of Formula X compounds wherein n and m are as defined above; O-L is an appropriate leaving group (e.g. alkoxy or phenoxy); and having a suitably disposed alkoxy group(s) (e.g. asterisk positions). Generally this deprotection/ cyclization is performed in a corollary fashion to the above described deprotection of Formula III, XII or VIII compounds to Formula I compounds.

According to Reaction Schemes I and II, Formula III compounds wherein R_9, n and m are as defined above may be prepared by alkylation/acylation of the appropriate Formula IV compounds wherein n, m and R_9 are as defined above with the appropriate Z_1-halogen compound.

Generally, the Formula IV compounds are exposed to a strong base such as metal hydrides, alkylamine metals or metal alkoxides at temperatures of -70°C to about ambient in a polar aprotic solvent such as ethereal solvents DMF or DMSO solvents. The appropriate Z_1-halogen compound is added to the above solution at a temperature of about -70°C to about 50°C for about 1 to 24 hours.

According to Reaction Scheme II, Formula IV compounds wherein n, m are as defined above and R_9 is H

may be prepared by cyclizing the appropriate Formula V compounds. Typically the cyclization occurs in the presence of a deoxygenating agent such as a trialkylphosphite at temperatures of ambient to 200°C preferably in an inert atmosphere such as nitrogen over 5 to 24 hours.

In a corollary fashion, for those Formula IV compounds wherein R_9 is halogen, the appropriate Formula V compound is first reacted with the appropriate halogen prior to the above cyclization. Generally the Formula V compound is exposed to the halogen in a suitable solvent at ambient temperatures and pressures (i.e. typical halogenation conditions).

According to Reaction Scheme II, Formula V compounds wherein n and m are as defined above may be prepared by coupling the appropriate Formula VI and VII compounds wherein n and m are as defined above. Typically the Formula VI compound is metalated with an alkyl or aryl metal such as n-butyl lithium in an aprotic solvent, preferablely diethyl ether, at temperatures of -80°C to -0°C. The resulting slurry is added to a -20°C to ambient temperature solution of zinc halide in an ethereal solvent (preferably THF). After a half hour to two hours the resulting solution is refluxed with the appropriate Formula VII compound in the presence of a catalytic amount of a zero valent transition metal such as palladium or nickel to yield the Formula V compound.

According to Reaction Scheme I and III compounds of Formula VIII wherein Z_3, n and m are as defined above may be prepared by alkylating the appropriate

Formula IX compounds wherein n and m are as defined above, with the appropriate Z_3-halogen compound.

Generally the Formula IX compounds are exposed to a base such as a metal hydride, metal alkoxide or alkylamine metal at temperatures of -70°C to ambient in a polar aprotic solvent such as DMF, DMSO or ethereal solvent at ambient pressures. The Z_3-halogen compound is added to the above solution at a temperature of about -70°C to about 50°C for about 1 to 24 hours time at ambient pressure.

According to Reaction Scheme III compounds of Formula IX wherein n and m are as defined above may be prepared by nitrating and reducing the appropriate Formula X compounds wherein n and m are as defined above and O-L is an appropriate leaving group (e.g. alkoxy, phenoxy). Typically the Formula X compound is nitrated with nitric acid under conventional nitrating conditions. The resulting compound is then reduced with, for example, zinc, iron/weak acid, palladium on carbon, hydrogen, etc. under standard reduction conditions.

According to Reaction Scheme III Formula X compounds wherein n, m and O-L are as defined above may be prepared by coupling the appropriate Formula VI and XI compounds wherein n, m and O-L are as defined above in a corollary fashion to the preparation of the Formula V compounds from Formula VI and VII compounds described earlier.

According to Reaction Schemes I and III Formula XII compounds wherein Z_2 is =N-phenyl-R_{10}; and n and m are as defined above may be prepared by iminizing the

appropriate Formula XIII compounds wherein n and m are as defined above with the appropriate primary amine. Generally the Formula XIII compound and appropriate amine are reacted as an intimate mixture with an acid catalyst, preferably a Lewis acid such as boron trifluoride etherate, at elevated temperatures of 150°C to 250°C for 1 to 6 hours at ambient pressures.

According to Reaction Scheme III compounds of Formula XIII wherein n and m are as defined above may be prepared from Formula X compounds wherein m, n and O-L are as defined above by an acid catalysis cyclization. Generally the Formula X compounds are added to a concentrated acid solution, preferably sulfuric, at ambient temperatures for 0.5 to 4 hours.

According to Reaction Scheme III Formula XII compounds wherein Z_2 is benzyl, hydroxybenzyl, $-CH_2$-pyridyl or $-CH_2$-quinolyl may be prepared from the corresponding Formula XII alkylidene compound by conventional hydrogenation using for example hydrogen in the presence of a catalyst such as palladium on carbon at elevated pressures and temperatures.

The corresponding Formula XII alkylidene compounds may be prepared from Formula XIII compounds wherein n and m are as defined above by reduction to the corresponding Formula XX methylene intermediate followed by condensation with the appropriate Z_2-CHO aldehyde compound. Generally, the Formula XIII compounds are reduced by conventional hydrogenation using for example hydrogen in the presence of a catalyst such as palladium on carbon at elevated pressures and temperatures. The resulting Formula XX

compounds are reacted in pyridine-type solvents in the presence of an alkylammonium base such as Triton B with the appropriate Z_2-CHO compound for 2 hours to 36 hours time at temperatures at ambient to 150°C at ambient pressure.

The starting materials for the above described reaction schemes (e.g. Formula VI, VII and XI compounds and the reagents Z_1-halogen, Z_3-halogen, Z_2-CHO or amines) can be easily synthesized by those skilled in the art starting from common chemical reagents using conventional methods of organic synthesis.

The compounds of this invention are acidic and they form base salts. All such base salts are within the scope of this invention and they can be prepared by conventional methods. For example, they can be prepared simply by contacting the acidic and basic entities, usually in a stoichiometric ratio, in either an aqueous, non-aqueous or partially aqueous medium, as appropriate. The salts are recovered either by filtration, by precipitation with a non-solvent followed by filtration, by evaporation of the solvent, or, in the case of aqueous solutions, by lyophilization, as appropriate.

The acyl prodrugs of the present phenolic compounds may be prepared by, for example, acylation of the tricyclic phenolic with the appropriate acid halide/anhydride in the presence of an organic amine base (e.g. pyridine, Et_3N).

The compounds of this invention are all readily adapted to therapeutic use as tyrosine kinase inhibitors for the control of tyrosine kinase dependent

diseases in mammals. Tyrosine kinase dependent diseases refer to hyperproliferative disorders which are initiated/ maintained by aberrant tyrosine kinase enzyme activity. Examples include cancer, atherosclerosis, angiogenic-based diseases (e.g., tumor growth, diabetic retinopathy), etc.

The in vitro tyrosine kinase inhibitory activity of the present compounds may be demonstrated by methods based on standard procedures. In one method the enzyme pp60src, a tyrosine-specific phosphokinase (tyrosine kinase) associated with the inner surface of the plasma membrane, is purified from Rous sarcoma virus-transformed rat cells. In the basis assay the enzyme is incubated with the substrate, val5 angiotensin II, and gamma-32p-ATP in a total volume of 25 µl for 25 minutes at 30°C according to Wong, T.W., Goldberg, A.R., J. Biol. Chem., 259, 8505-8512 (1984). The reaction is terminated by the addition of 45 µl of 5% TCA, incubated on ice for 5 minutes and centrifuged for 1 minute to remove precipitated protein. 35 µl aliquots of the supernatants are applied to phosphocellular paper circles, which are then washed in 3 changes of 0.5% H_3PO_4, acetone-rinsed, dried and counted by liquid scintillation. For screening, the compound to be tested is included in the 25 µl incubation mixture; compounds are tested at 10-4M, 10-5M and 10-6M and appropriate solvent controls are included in all assays.

The compounds are administered either orally or parenterally, or topically as eye drops, in dosages ranging from about 0.1 to 10 mg/kg of body weight per

day in single or divided doses. Of course, in particular situations, at the discretion of the attending physician, doses outside of this range will be used.

The compounds of this invention can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically-acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, elixirs, syrups, injectable or eye drop solutions, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents.

For purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate are employed along with various disintegrants such as starch and preferably potato or tapioca starch, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type are also employed as fillers in soft and hard-filled gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the essential active ingredient therein can be combined with various sweetening agents, flavoring agents,

coloring agents, emulsifying agents and/or suspending agents, as well as such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For purposes of parenteral administration, solutions in sesame or peanut oil or in aqueous propylene glycol can be employed, as well as sterile aqueous solutions of the corresponding water-soluble, alkali metal or alkaline-earth metal salts previously enumerated. Such aqueous solutions should be suitable buffered, if necessary, and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal injection purposes. In this connection, the sterile aqueous media employed are all readily obtainable by standard techniques well-known to those skilled in the art.

For purposes of topical administration, dilute sterile, aqueous solutions (usually in about 0.1% to 5% concentration), otherwise similar to the above parenteral solutions, are prepared in containers suitable for dropwise administration to the eye.

In a pharmaceutical composition comprising a compound of formula I, or a pharmaceutically-acceptable salt thereof, the weight ratio of carrier to active ingredient will normally be in the range from 1:4 to 4:1, and preferably 1:2 to 2:1. However, in any given case, the ratio chosen will depend on such factors as the solubility of the active component, the dosage contemplated and the precise route of administration.

EXAMPLE 1

5-Phenylmethyl-2,3,8,9-tetrahydroxy-6(5H)-phenanthridinone - To a cooled (0°C), stirred solution of 5-phenylmethyl-2,3,8,9-tetramethoxy-6(5H)-phenanthridinone (0.50 g, 1.23 mmol) in dichloromethane (12 mL) was added boron tribromide (0.58 mL, 6.17 mmol) dropwise. The reaction mixture was allowed to stir at room temperature for 2 hours, poured into ice water and extracted with EtOAc. The organic phase was washed with water, brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was recrystallized from MeOH/CCl_4 to afford the title compound (0.30 g); m.p. 261-263°C. Anal. Calcd. for $C_{20}H_{15}NO_5 \cdot 0.5H_2O$: C, 67.03; H, 4.50; N, 3.91. Found: C, 67.24; H, 3.91; N, 3.90.

The following compounds Examples (2-92) were prepared from the appropriate starting material using the above general procedure:

2,3,8,9-Tetrahydroxy-6(5H)-phenanthridinone; m.p. >250°C. Anal. Calcd. for $C_{13}H_9NO_5.1.3H_2O$: C, 55.14; H, 4.15; N, 4.95. Found: C, 54.83; H, 3.71; N, 4.85.

2,3,7,8-Tetrahydroxy-6(5H)-phenanthridinone; m.p. >360°C. Anal. Calcd. for $C_{13}H_9NO_5$: C, 60.25; H, 3.50; N, 5.41. Found: C, 56.76; H, 3.50; N, 4.82.

2,3-Dihydroxy-6(5H)-phenanthridinone; m.p. 112-113°C.

8,9-Dihydroxy-6(5H)-phenanthridinone; m.p. 311°C dec. (acetone). Anal. Calcd. for $C_{13}H_9NO_3$: C, 68.72; H, 3.99; N, 6.17. Found: C, 67.98; H, 3.78; N, 5.81.

5-Phenylmethyl-2,3,7,8-tetrahydroxy-6(5H)-phenanthridinone; m.p. 224-225°C (MeOH/CCl_4). Anal.

Calcd. for $C_{20}H_{15}NO_5.0.75H_2O$: C, 66.20; H, 4.58; N, 3.86. Found: C, 66.52; H, 4.40; N, 3.86.

5-Ethyl-2,3,8,9-tetrahydroxy-6(5H)-phenanthridinone; m.p. 309-310°C (MeOH/CCl_4). Anal. Calcd. for $C_{15}H_{13}NO_5.0.5H_2O$: C, 60.81; H, 4.76; N, 4.27. Found: C, 60.56; H, 4.98; N, 4.17.

5-Ethyl-2,3,7,8-tetrahydroxy-6(5H)-phenanthridinone; m.p. 275°C (acetone/hexanes). Anal. Calcd. for $C_{15}H_{13}NO_5.1H_2O$: C, 59.01; H, 4.95; N, 4.59. Found: C, 58.70; H, 4.65; N, 4.38.

5-((4-Nitrophenyl)methyl)-2,3,7,8-tetrahydroxy-6(5H)phenanthridinone; m.p. 258-263°C (MeOH/CCl_4). Anal. Calcd. for $C_{20}H_{14}N_2O_7.0.75H_2O$: C, 58.90; H, 3.83; N, 6.87. Found: C, 58.88; H, 3.77; N, 6.84.

5-((4-Nitrophenyl)methyl)-2,3,8,9-tetrahydroxy-6(5H)-phenanthridinone; m.p. 325°C dec (MeOH/CCl_4). Anal. Calcd. for $C_{20}H_{14}N_2O_7.0.75H_2O$: C, 58.90; H, 3.83; N, 6.87. Found: C, 58.88; H, 3.32; N, 6.83.

5-((3,4-Dichlorophenyl)methyl)-2,3,7,8-tetrahydroxy-6(5H)-phenanthridinone; m.p. 246°C (MeOH/CCl_4). Anal. Calcd. for $C_{20}H_{13}Cl_2NO_5.0.5H_2O$: C, 56.23; H, 3.30; N, 3.28. Found: C, 56.51; H, 2.98; N, 3.28.

5-((3,4-Dichlorophenyl)methyl)-2,3,8,9-tetrahydroxy-6(5H)-phenanthridinone; m.p. 318°C (MeOH/CCl_4). Anal. Calcd. for $C_{20}H_{13}Cl_2NO_5.0.5H_2O$: C, 56.23; H, 3.30; N, 3.28. Found: C, 56.36; H, 2.95; N, 3.14.

5-(((4-Phenylsulfonyl)phenyl)methyl)-2,3,7,8-tetrahydroxy-6(5H)-phenanthridinone; m.p. 305-307°C (MeOH/CCl_4). Anal. Calcd. for $C_{26}H_{19}NO_7S.0.5H_2O$: C, 62.65; H, 4.04; N, 2.81. Found: C, 62.53; H, 3.65; N, 2.83.

5-(((4-Phenylsulfonyl)phenyl)methyl)-2,3,8,9-tetrahydroxy-6(5H)-phenanthridinone; m.p.245-251°C (MeOH/CCl_4).

5-((4-Hydroxyphenyl)methyl-2,3,8,9-tetrahydroxy-6(5H)-phenanthridinone; m.p. 168°C (MeOH/CCl_4). Anal. Calcd. for $C_{20}H_{15}NO_6$:1.5H_2O: C, 61.23; H, 4.24; N. 3.57. Found: C, 61.49; H, 4.50; N, 3.50.

5-((3-Phenyl)propyl)-2,3,8,9-tetrahydroxy-6(5H)-phenanthridinone; m.p. 155-158°C (MeOH/CCl_4).

1,2-Dihydroxyfluoren-9-one; m.p. 184-185°C (EtOAc/hexanes). Anal. Calcd. for $C_{13}H_8O_3$: C, 73.58; H, 3.80. Found: C, 73.18; H, 3.64.

2,3-Dihydroxyfluoren-9-one; m.p. 228-230°C (EtOAc/hexanes). Anal. Calcd. for $C_{13}H_8O_3$.0.25H_2O: C, 72.81; H, 3.88. Found: C, 72.83; H, 3.84.

2,3,6,7-Tetrahydroxyfluoren-9-one; m.p. >250°C. Anal. Calcd. for $C_{13}H_8O_5$.0.3H_2O: C, 62.40; H, 3.47. Found: C, 62.17; H, 3.37.

1,2,6,7-Tetrahydroxyfluoren-9-one; m.p. 304°C dec. (MeOH/$CHCl_3$). Anal. Calcd. for $C_{13}H_8O_5$: C, 63.95; H, 3.30. Found: C, 63.51; H, 3.12.

1,2-Dihydroxy-9H-fluorene; m.p. 159-162°C (EtOAc/cyclohexane).

2,3-Dihydroxy-9H-fluorene; m.p. 155-156°C (EtOAc/cyclohexane).

2,3,6,7-Tetrahydroxy-9H-fluorene; m.p. >250°C. Anal. Calcd. for $C_{13}H_{10}O_4$.0.25H_2O: C, 66.52; H, 4.51. Found: C, 66.69; H, 4.29.

9-(Phenylmethylene)-1,2-dihydroxyfluorene; m.p. 139-141°C. Anal. Calcd. for $C_{20}H_{14}O_2$.0.33H_2O: C, 82.17; H, 5.06. Found: C, 81.93; H, 4.99.

9-(Phenylmethylene)-2,3,6,7-tetrahydroxyfluorene; foam. 1H NMR (d_6-DMSO) delta 9.04 (br s, 1H), 9.01 (br s, 1H), 8.77 (br s, 1H), 8.61 (br s, 1H), 7.52-7.28 (m, 5H), 7.19 (s, 1H), 7.10 (s, 1H), 6.92 (s, 1H), 6.85 (s, 1H), 6.83 (s, 1H).

9-(Phenylmethyl)-2,3,6,7-tetrahydroxyfluorene; m.p. 230°C dec. Anal. Calcd. for $C_{20}H_{16}O_4.0.25H_2O$: C, 73.95; H, 5.12. Found: C, 74.04; H, 5.02.

9-(Phenylmethyl)-1,2-dihydroxyfluorene; m.p. 134-136°C.

9-(Phenylmethyl)-1,2,6,7-tetrahydroxyfluorene; m.p. 233-235°C (EtOAc/hexanes). Anal. Calcd. for $C_{20}H_{16}O_4.0.1H_2O$: C, 74,57; H, 5.07. Found: C, 74.45; H, 4.72.

9-((4-Hydroxyphenyl)methylene)-2,3,6,7-tetrahydroxyfluorene; m.p. 210°C dec. Anal. Calcd. for $C_{20}H_{14}O_5$: C, 71.86; H, 4.22. Found: C, 67.66; H, 4.02.

9-((4-Hydroxyphenyl)methylene)-1,2,6,7-tetrahydroxyfluorene; m.p. 228-230°C (MeOH/H_2O). Anal. Calcd. for $C_{20}H_{14}O_5.0.5H_2O$: C, 69.97; H, 4.40. Found: C, 69.84; H, 4.30.

9-((4-Hydroxyphenyl)methyl)-2,3,6,7-tetrahydroxyfluorene; m.p. 314-316°C. Anal. Calcd. for $C_{20}H_{16}O_5.0.25H_2O$: C, 70.48; H, 4.88. Found: C, 70.26; H, 4.59.

9-((4-Pyridyl)methylene)-1,2-dihydroxyfluorene; m.p. 250°C dec (MeOH/$CHCl_3$).

9-((4-Pyridyl)methyl)-1,2-dihydroxyfluorene; m.p. 263°C dec.

9-((4-Pyridyl)methyl)-2,3,6,7-tetrahydroxy-fluorene; m.p. 240°C dec. (MeOH/$CHCl_3$). Anal. Calcd. for $C_{19}H_{15}NO_4 \cdot 0.5H_2O$: C, 68.15; H, 4.97. Found: C, 68.57; H, 4.75.

9-(((4-Trifluoromethyl)phenyl)methylene)-2,3,6,7-tetrahydroxyfluorene; m.p. 228°C. Anal. Calcd. for $C_{21}H_{13}F_3O_4 \cdot 0.5H_2O$: C, 63.80; H, 3.57. Found: C, 64.11; H, 3.55.

9-((4-Quinolyl)methylene)-2,3,6,7-tetrahydroxy-fluorene; m.p. >320°C.

9-((4-Quinolyl)methylene)-1,2-dihydroxyfluorene; m.p. 315°C (MeOH).

9-((4-Quinolyl)methylene)-1,2,6,7-tetrahydroxy-fluorene; m.p. >350°C.

9-((4-Quinolyl)methyl)-1,2-dihydroxyfluorene; m.p. 244-246°C (MeOH/$CHCl_3$).

9-((4-Quinolyl)methyl)-2,3,6,7-tetrahydroxy-fluorene; m.p. 240°C dec.

1,2,6,7-Tetrahydroxy-9H-carbazole; m.p. >280°C (H_2O). Anal. Calcd. for $C_{12}H_9NO_4$: C, 62.34; H, 3.92; N, 6.06. Found: C, 62.01; H, 3.83; N, 6.03.

2,3-Dihydroxy-9H-carbazole; m.p. 279-283°C (MeOH/H_2O). Anal. Calcd. for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.11; H, 4.49; N, 6.97.

2,3,6,7-Tetrahydroxy-9H-carbazole; m.p. >300°C (H_2O). Anal. Calcd. for $C_{12}H_9NO_4 \cdot 0.2H_2O$: C, 61.38; H, 4.03; N, 5.97. Found: C, 61.76; H, 3.77; N, 5.98.

9-Benzoyl-1,2,6,7-tetrahydroxycarbazole; m.p. 242-243°C (MeOH/H_2O). Anal. Calcd. for $C_{19}H_{13}NO_5$: C, 68.05; H, 3.91; N, 4.18. Found: C, 67.71; H, 3.68; N, 4.19.

9-Benzoyl-2,3-dihydroxycarbazole; m.p. 260-261°C ($EtOH/H_2O$). Anal. Calcd. for $C_{19}H_{13}NO_3.0.25H_2O$: C, 74.13; H, 4.41; N, 4.55. Found: C, 74.52; H, 4.05; N, 4.51.

9-Benzoyl-2,3,6,7-tetrahydroxycarbazole; m.p. 287-292°C ($MeOH/H_2O$). Anal. Calcd. for $C_{19}H_{13}NO_5.1H_2O$: C, 64.58; H, 4.27; N, 3.96. Found: C, 64.74; H, 3.97; N, 3.94.

9-(Phenylmethyl)-1,2,6,7-tetrahydroxycarbazole; m.p. 241-246°C ($MeOH/H_2O$). Anal. Calcd. for $C_{19}H_{15}NO_4.0.25H_2O$: C, 70.03; H, 4.80; N, 4.30. Found: C, 70.32; H, 4.52; N. 4.07.

9-(Phenylmethyl)-2,3,6,7-tetrahydroxycarbazole; m.p. 266-271°C ($MeOH/H_2O$). Anal. Calcd. for $C_{19}H_{15}NO_4.0.25H_2O$: C, 70.03; H, 4.80; N, 4.30. Found: C, 70.02; H, 4.47; N, 4.37.

9-Methyl-2,3,6,7-tetrahydroxycarbazole; m.p. >270°C (H_2O). Anal. Calcd. for $C_{13}H_{11}NO_4.0.25H_2O$: C, 62.51; H, 4.63; N, 5.60. Found: C, 62.56; H, 4.37; N, 5.62.

9-(Methylsulfonyl)-1,2,6,7-tetrahydroxycarbazole; m.p. 211-213°C dec. (EtOAc/hexanes). Anal. Calcd. for $C_{13}H_{11}NO_6S$: C, 50.48; H, 3.59; N, 4.53. Found: C, 50.25; H, 3.47; N, 4.25.

9-(Methylsulfonyl)-2,3,6,7-tetrahydroxycarbazole; m.p. 278-280°C ($MeOH/H_2O$). Anal. Calcd. for $C_{13}H_{11}NO_6S$: C, 50.48; H, 3.59; N, 4.53. Found: C, 50.58; H, 3.29; N, 4.55.

9-(Phenylsulfonyl)-1,2,6,7-tetrahydroxycarbazole; m.p. 176-178°C ($MeOH/H_2O$). Anal. Calcd. for

$C_{18}H_{13}NO_6S.0.4H_2O$: C, 57.02; H, 3.68; N, 3.69. Found: C, 56.70; H, 3.33; N, 3.67.

9-(Phenylsulfonyl)-2,3,6,7-tetrahydroxycarbazole; m.p. 240-241°C (MeOH/H_2O). Anal. Calcd. for $C_{18}H_{13}NO_6S.1H_2O$: C, 55.52; H, 3.88; N, 3.59. Found: C, 55.44; H, 3.45; N, 3.36.

9-(4-t-Butylbenzoyl)-1,2,6,7-tetrahydroxycarbazole; m.p. 234-236°C (MeOH/H_2O). Anal. Calcd. for $C_{23}H_{21}NO_5$: C, 70.57; H, 5.36; N, 3.58. Found: C, 70.30; H, 5.36; N, 3.59.

9-((4-Trifluoromethyl)benzoyl)-1,2,6,7-tetrahydroxycarbazole: m.p. 229-230°C (EtOAc/hexanes). Anal. Calcd. for $C_{20}H_{12}F_3NO_5.0.4H_2O$: C, 58.51; H, 3.14; N, 3.41. Found: C, 58.77; H, 2.91; N, 3.37.

9-((4-Methylsulfonyl)benzoyl)-1,2,6,7-tetrahydroxycarbazole; m.p. 286-288°C (acetone/CH_2Cl_2). Anal. Calcd. for $C_{20}H_{15}NO_7S$: C, 58.10; H, 3.66; N, 3.39. Found: C, 58.06; H, 3.56; N, 3.39.

9-(4-Bromobenzoyl)-1,2,6,7-tetrahydroxycarbazole; m.p. 272-278°C (EtOAc/hexanes). Anal. Calcd. for $C_{19}H_{12}BrNO_5$: C, 55.09; H, 2.92; N, 3.38. Found: C, 54.80; H, 2.72; N, 3.64.

9-(4-Phenylbenzoyl)-1,2,6,7-tetrahydroxycarbazole; m.p. 291-294°C (EtOAc). Anal. Calcd. for $C_{25}H_{17}NO_5.0.25H_2O$: C, 72.19; H, 4.24; N, 3.37. Found: C, 72.32; H, 4.02; N, 3.28.

9-(3-Phenylpropionyl)-1,2,6,7-tetrahydroxycarbazole; m.p. 223-227°C (EtOAc/hexanes). Anal. Calcd. for $C_{21}H_{17}NO_5$: C, 69.41; H, 4.71; N, 3.86. Found: C, 69.11; H, 4.52; N, 3.84.

9-(2-Napthoyl)-1,2,6,7-tetrahydroxycarbazole; m.p. 266-270°C (EtOAc). Anal. Calcd. for $C_{23}H_{15}NO_5.0.15H_2O$: C, 71.21; H, 3.97; N, 3.61. Found: C, 71.30; H, 3.88; N, 3.61.

9-(3-Nitrobenzoyl)-1,2,6,7-tetrahydroxycarbazole; m.p. 275-279°C (EtOAc). Anal. Calcd. for $C_{19}H_{12}N_2O_7$: C, 60.00; H, 3.18; N, 7.36. Found: C, 59.73; H, 2.90; N, 7.22.

9-(3-Pyridylmethyl)-2,3,6,7-tetrahydroxycarbazole; m.p. 290-294°C (MeOH/H_2O). Anal. Calcd. for $C_{18}H_{14}N_2O_4.HBr.0.5H_2O$: C, 52.44; H, 3.67; N, 6.80. Found: C, 52.23; H, 3.94; N, 6.83.

9-((3-Methylphenyl)methyl)-1,2,6,7-tetrahydroxycarbazole; m.p. 150-155°C dec (EtOAc/hexanes). Anal. Calcd. for $C_{20}H_{17}NO_4$: C, 71.63; H, 5.11; N, 4.18. Found: C, 71.78; H, 5.11; N, 3.96.

9-((4-Cyanophenyl)methyl)-1,2,6,7-tetrahydroxycarbazole; m.p. 225-227°C (MeOH/H_2O). Anal. Calcd. for $C_{20}H_{14}N_2O_4.0.25H_2O$: C, 68.46; H, 4.13; N, 8.00. Found: C, 68.74; H, 3.75; N, 8.40.

9-((4-Trifluoromethylphenyl)methyl)-1,2,6,7-tetrahydroxycarbazole; m.p. 266-270°C (MeOH/H_2O). Anal. Calcd. for $C_{20}H_{14}F_3NO_4.0.25H_2O$: C, 60.99; H, 3.68; N, 3.56. Found: C, 60.80; H, 3.41; N, 3.62.

9-((2,6-Dichlorophenyl)methyl)-1,2,6,7-tetrahydroxycarbazole; m.p. 263-265°C (EtOAc). Anal. Calcd. for $C_{19}H_{13}Cl_2NO_4$: C, 58.48; H, 3.36; N, 3.59. Found: C, 58.34; H, 3.29; N, 3.53.

9-((4-Phenylsulfonyl)phenylmethyl)-1,2,6,7-tetrahydroxycarbazole; m.p. >300°C (EtOAc/hexanes). Anal.

Calcd. for $C_{25}H_{19}NO_6S$: C, 63.09; H, 4.36; N, 2.94. Found: C, 62.92; H, 3.96; N, 3.01.

9-(4-Bromophenylmethyl)-1,2,6,7-tetrahydroxycarbazole; m.p. 249-252°C (MeOH/H_2O). Anal. Calcd. for $C_{19}H_{14}BrNO_4.0.25H_2O$: C, 56.38; H, 3.61; N, 3.46. Found: C, 56.33; H, 3.36; N, 3.35.

9-(3-Phenylpropyl)-1,2,6,7-tetrahydroxycarbazole; m.p. 246-252°C (MeOH/CH_2Cl_2). Anal. Calcd. for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 71.89; H, 5.23; N, 3.95.

9-((Phenylmethyl)sulfonyl)-1,2,6,7-tetrahydroxycarbazole; m.p. 216-218°C (MeOH/H_2O). Anal. Calcd. for $C_{19}H_{15}NO_6S$: C, 59.21; H, 3.92; N, 3.64. Found: C, 59.10; H, 3.64; N, 3.77.

9-((2,5-Dichlorophenyl)sulfonyl)-1,2,6,7-tetrahydroxycarbazole; m.p. >300°C (MeOH/H_2O). Anal. Calcd. for $C_{18}H_{11}Cl_2NO_6S.0.25H_2O$: C, 48.60; H, 2.60; N, 3.15. Found: C, 48.67; H, 2.45; N, 3.17.

9-((4-Nitrophenyl)sulfonyl)-1,2,6,7-tetrahydroxycarbazole; m.p. 233-234°C (MeOH/H_2O). Anal. Calcd. for $C_{18}H_{12}N_2O_8S.0.25H_2O$: C, 51.36; H, 2.99; N, 6.66. Found: C, 51.16; H, 2.81; N, 6.53.

4-Bromo-1,2,6,7-tetrahydroxy-9H-carbazole; m.p. >260°C (acetone/CH_2Cl_2). Anal. Calcd. for $C_{12}H_8BrNO_4$: C, 46.47; H, 2.60; N, 4.52. Found: C, 46.47; H, 2.62; N, 4.45.

9-((4-Trifluoromethyl)benzoyl)-4-bromo-1,2,6,7-tetrahydroxycarbazole; m.p. 228-230°C (EtOAc/hexanes). Anal. Calcd. for $C_{20}H_{11}BrF_3NO_5$: C, 49.81; H, 2.30; N, 2.91. Found: C, 49.78; H, 2.10; N, 2.89.

9-((4-Methylsulfonyl)benzoyl)-4-bromo-1,2,6,7-tetrahydroxycarbazole; m.p. >280°C (MeOH). Anal. Calcd. for $C_{20}H_{14}BrNO_7S$: C, 48.79; H, 2.87; N, 2.85. Found: C, 48.42; H, 2.84; N, 2.80.

9-(4-t-Butylbenzoyl)-4-bromo-1,2,6,7-tetrahydroxycarbazole; m.p. >280°C (MeOH/H_2O). Anal. Calcd. for $C_{23}H_{20}BrNO_5$: C, 58.73; H, 4.29; N, 2.98. Found: C, 58.94; H, 4.26; N, 2.95.

9-((4-Cyanophenyl)methyl)-4-bromo-1,2,6,7-tetrahydroxycarbazole; m.p. >260°C (MeOH/CH_2Cl_2). Anal. Calcd. for $C_{20}H_{13}BrN_2O_4$: C, 56.49; H, 3.08; N, 6.59. Found: C, 56.24; H, 3.09; N, 6.47.

9-(Methylsulfonyl)-4-bromo-1,2,6,7-tetrahydroxycarbazole; m.p. >270°C (MeOH/H_2O). Anal. Calcd. for $C_{13}H_{10}BrNO_6S$: C, 40.22; H, 2.60; N, 3.61. Found: C, 43.32; H, 3.25; N, 3.39.

N-9H-1,2,6,7-Tetrahydroxyfluoren-9-ylidene-benzamine; m.p. 235-239°C (isopropyl alcohol/hexane). Anal. Calcd. for $C_{19}H_{13}NO_4.0.5H_2O$: C, 69.51; H, 4.30; N, 4.27. Found: C, 69.26; H, 3.90; N, 4.00.

N-9H-2,3,6,7-Tetrahydroxyfluoren-9-ylidene-benzamine; m.p. 184-187°C. Anal. Calcd. for $C_{19}H_{13}NO_4.1.25H_2O$: C, 66.76; H, 4.57; N, 4.10. Found: C, 66.92; H, 4.33; N, 3.36.

N-9H-2,3,6,7-Tetrahydroxyfluoren-9-ylidene-(4'-cyano)benzamine; m.p. >350°C (acetone/MeOH/H_2O). Anal. Calcd. for $C_{20}H_{12}N_2O_4.0.25H_2O$: C, 68.86; H, 3.61; N, 8.03. Found: C, 68.71; H, 3.33; N, 7.37.

N-9H-2,3,6,7-Tetrahydroxyfluoren-9-ylidene-(4'-trifluoromethyl)benzamine; m.p. 168-172°C (EtOAc/cyclohexane). Anal. Calcd. for

$C_{20}H_{12}F_3NO_4.0.25H_2O$: C, 61.30; H, 3.22; N, 3.58. Found: C, 61.27; H, 3.23; N, 3.34.

N-9H-1,2,6,7-Tetrahydroxyfluoren-9-ylidene-(3,5-dichloro)benzamine; m.p. 258-260°C (EtOAc/hexanes). Anal. Calcd. for $C_{19}H_{11}Cl_2NO_4$: C, 58.79; H, 2.86; N, 3.61. Found: C, 58.57; H, 2.80; N, 3.53.

N-9H-1,2,6,7-Tetrahydroxyfluoren-9-ylidene-(4'-nitro)benzamine; m.p. 254-256°C (dioxane/hexanes). Anal. Calcd. for $C_{19}H_{12}N_2O_6.0.5H_2O$: C, 61.13; H, 3.50; N, 7.51. Found: C, 61.28; H, 3.72; N, 6.82.

N-9H-1,2,6,7-Tetrahydroxyfluoren-9-ylidene-(4'-i-propyl)benzamine; m.p. 147-150°C. Anal. Calcd. for $C_{22}H_{19}NO_4.0.5H_2O$: C, 71.34; H, 5.44; N, 3.78. Found: C, 71.67; H, 5.44; N, 3.65.

N-9H-1,2,6,7-Tetrahydroxyfluoren-9-ylidene-(4'-methylsulfonyl)benzamine; m.p. 168°C dec. (dioxane/hexanes). Anal. Calcd. for $C_{20}H_{15}NO_6S$: C, 60.46; H, 3.81; N, 3.53. Found: C, 58.85; H, 4.83; N, 2.75.

3,4-Dihydroxy-6H-dibenzo[b,d]pyran-6-one; m.p. 254-256°C (EtOH).

7,8-Dihydroxy-6H-dibenzo[b,d]pyran-6-one; m.p. 185-187°C (EtOAc/cyclohexane).

8,9-Dihydroxy-6H-dibenzo[b,d]pyran-6-one; m.p. >255°C (EtOAc).

2,3,8,9-Tetrahydroxy-6H-dibenzo[b,d]pyran-6-one; m.p. >250°C.

3,4,8,9-Tetrahydroxy-6H-dibenzo[b,d]pyran-6-one; m.p. >250°C (EtOH). Anal. Calcd. for $C_{13}H_8O_6$: C, 60.00; H, 3.10. Found: C, 59.66; H, 2.85.

3,4,7,8-Tetrahydroxy-6H-dibenzo[b,d]pyran-6-one; m.p. >280°C. Anal. Calcd. for $C_{13}H_8O_6 \cdot 0.25H_2O$: C, 58.99; H, 3.23. Found: C, 59.32; H, 3.20.

PREPARATION 1

A

4,5-Dimethoxy-2-((2,4,5-trimethoxy)phenyl)benzonitrile - To a cooled (-78°C), stirred solution of 2,4,5-trimethoxybromobenzene (6.63 g, 27.0 mmol) in ether (25 mL) was added dropwise a 2.5M solution of n-butyllithium (10.7 mL, 27 mmol) in hexanes. After 10 minutes, the slurry was allowed to warm to 0°C and THF (20 mL) was added. The resulting solution was added via a cannula to a cooled (0°C), stirred solution of fused zinc chloride (4.39 g, 32.0 mmol) in THF (50 mL) and this solution was maintained at 0°C for 1 hour.

To a slurry of bis(triphenylphosphine)palladium (II) chloride (0.3 g, 0.4 mmol) in THF (20 mL) was added a 1M solution of diisobutylaluminum hydride (0.8 mL, 0.8 mmol) and the resulting black solution was stirred at ambient temperature for 20 minutes. A solution of 2-bromo-4,5-dimethoxybenzonitrile (5.0 g, 21 mmol) in THF (20 mL) and the solution of the organozinc reagent were added to the palladium catalyst. The resulting dark solution was refluxed for 18 hours, diluted into EtOAc, washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo to afford a dark oil. Flash chromatography (30% EtOAc/hexanes) afforded the title compound (4.0 g); m.p. 154-156°C (EtOH). Anal. Calcd. for $C_{18}H_{19}NO_5$: C, 65.65; H, 5.82; N, 4.25. Found: C, 65.28; H, 5.78; N, 3.42.

The following compounds (B-H) were prepared using the above general procedure:

Methyl 2,3-dimethoxy-6-((3,4,5-trimethoxy)phenyl)-benzoate; m.p. 94-97°C. Anal. Calcd. for $C_{19}H_{22}O_7$: C, 62.97; H, 6.12. Found: C, 63.09; H, 6.05.

Ethyl 2-((3,4-dimethoxy)phenyl)-4,5-dimethoxy-benzoate; m.p. 91-94°C. Anal. Calcd. for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40. Found: C, 65.72; H, 6.45.

Ethyl 2,3-dimethoxy-6-((3,4-dimethoxy)phenyl)-benzoate; m.p. 76-77°C (acetone/hexanes). Anal. Calcd. for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40. Found: C, 65.98; H, 6.15.

2-((3,4-Dimethoxy)phenyl)-4,5-dimethoxynitro-benzene; m.p. 149-151°C (EtOH). Anal. Calcd. for $C_{16}H_{17}NO_6$: C, 60.18; H, 5.37; N, 4.39. Found: C, 60.27; H, 5.35; N, 4.39.

4,5-Dimethoxy-2-phenylnitrobenzene; m.p. 113-115°C (MeOH/H_2O). Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.50; N, 5.40. Found: C, 64.88; H, 5.06; N, 5.29.

Ethyl 2-((3,4-dimethoxy)phenyl)benzoate; m.p. 71-75°C.

Methyl 2,3-dimethoxy-6-((2-methoxy)phenyl)-benzoate; m.p. oil. Rf (silica) = 0.43 (30% ethyl acetate/hexanes).

PREPARATION 2

(2,3-Dimethoxy)phenyl 2-bromo-4,5-dimethoxy-benzoate - To a stirred solution of 2-bromo-4,5-dimethoxybenzoyl chloride (5.4 g, 21 mmol) in CH_2Cl_2 (50 mL) was added triethylamine (5.9 mL, 42 mmol) and 2,3-dimethoxyphenyl (5.4 mL, 25 mmol) dropwise over 5 minutes. The reaction was stirred for 2 hours, diluted

into EtOAc, washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The resulting solids were recrystallized from EtOH to afford the title compound as a colorless solid (6.2 g); m.p. 103-105°C.

PREPARATION 3

3,4,8,9-Tetramethoxy-6H-dibenzo[b,d]pyran-6-one - A stirred mixture of (2,3-Dimethoxy)phenyl 2-bromo-4,5-dimethoxybenzoate (5.0 g, 13 mmol), sodium acetate (2.1 g, 25 mmol) and bis(triphenylphosphine)palladium (II) chloride (0.9 g, 1.3 mmol) in N,N-dimethylacetamide (75 mL) was maintained at 120°C for 23 hours. The reaction mixture was cooled, poured onto brine, acidified (pH = 1) with 1N HCl and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The resulting solids were recrystallized from EtOAc to afford the title compound (0.8 g); m.p. 222-223°C.

PREPARATION 4

A

Ethyl 4,5-dimethoxy-2-((4,5-dimethoxy-2-nitro)-phenyl)benzoate - To a stirred solution of ethyl 2-((3,4-dimethoxy)phenyl)-4,5-dimethoxybenzoate (2.00 g, 5.77 mmol) in glacial acetic acid (30 mL) was added concentrated nitric acid (0.72, 11.5 mmol) dropwise. After 10 minutes, the reaction mixture was poured onto ice (150 g) and the solids were extracted into EtOAc. The organic phase was washed with water, 1N NaOH, brine, dried (Na_2SO_4), filtered and concentrated in vacuo to afford the title compounds as a yellow solid (2.25 g); m.p. 126-128°C. Anal. Calcd.

for $C_{19}H_{21}NO_8$: C, 58.30; H, 5.41; N, 3.58. Found: C, 57.80; H, 5.40; N, 3.71.

The following compounds (B-C) were prepared from the appropriate starting material using the above general procedure:

Ethyl 2,3-dimethoxy-6-((4,5-dimethoxy-2-nitro)-phenyl)benzoate; m.p. 118-120°C. Anal. Calcd. for $C_{19}H_{21}NO_8$: C, 58.30; H, 5.41; N, 3.58. Found: C, 58.28; H, 5.28; N, 3.49.

Ethyl 2-(((4,5-dimethoxy)-2-nitro)phenyl)benzoate.

PREPARATION 5

A

2,3,8,9-Tetramethoxy-6(5H)-phenanthridinone - To a stirred, heated (100°C) slurry of iron dust (325 mesh, 2.8 g) in glacial acetic acid (30 mL) was added a solution of ethyl 4,5-dimethoxy-2-((4,5-dimethoxy-2-nitro)phenyl)benzoate (1.42 g, 3.63 mmol) in glacial acetic acid (40 mL) was added over 5 minute period. After 1.5 hours, the residual iron fillings were removed with a magnetic stir bar and the reaction slurry was poured onto ice/water (150 mL). The solids were filtered, washed with water, air-dried and dried in vacuo at 80°C to afford the title compound as a gray solid (1.00 g); m.p. >250°C.

The following compounds (B-C) were preapred from the appropriate starting material using the above general procedure:

2,3-Dimethoxy-6(5H)-phenanthridinone; m.p. 253-255°C (acetone/cyclohexane).

2,3,7,8-Tetramethoxy-6(5H)-phenanthridinone; ^1H NMR (d_6-DMSO) delta 8.10 (d, 1H), 7.62 (s, 1H), 7.47

(d, 1H), 6.81 (s, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.75 (s, 3H), 3.73 (s, 3H).

PREPARATION 6

A

5-Phenylmethyl-2,3,8,9-tetramethoxy-6(5H)-phenanthridinone - To a slurry of 2,3,8,9-Tetramethoxy-6(5H)-phenanthridinone (0.6 g, 1.9 mmol) in anhydrous dimethyl sulfoxide (10 mL) was added potassium t-butoxide (0.32 g, 2.85 mmol) and the resulting brown solution was stirred at room temperature for 15 minutes. After the addition of benzyl bromide (0.6 g, 3.8 mmol), the reaction mixture was allowed to stir for 1 hour. The reaction was poured into 1N HCl and extracted with EtOAc. The organic phase was washed with water, brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was flash chromatographed (30% EtOAc/hexanes) to afford the title compound (0.54 g); m.p. 214-215°C ($CHCl_3$/hexanes). Anal. Calcd. for $C_{24}H_{23}NO_5$: C, 71.10; H, 5.72; N, 3.46. Found: C, 69.15; H, 5.65; N, 3.25.

The following compounds (B-L) were prepared from the appropriate starting material using the above general procedure:

5-Ethyl-2,3,8,9-tetramethoxy-6(5H)-phenanthridinone; m.p. 191-192°C. Anal. Calcd. for $C_{19}H_{21}NO_5$: C, 66.47; H, 6.17; N, 4.08. Found: C, 65.96; H, 6.31; N, 4.03.

5-((3,4-Dichlorophenyl)methyl)-2,3,8,9-tetramethoxy-6(5H)-phenanthridinone; 225-226°C. Anal. Calcd. for $C_{24}H_{21}Cl_2NO_5$: C, 60.78; H, 4.46; N, 2.95. Found: C, 60.44; H, 4.29; N, 2.95.

5-(((4-Phenylsulfonyl)phenyl)methyl)-2,3,8,9-tetramethoxy-6(5H)-phenanthridinone; m.p. 245-246°C ($CHCl_3$/MeOH). Anal. Calcd. for $C_{30}H_{27}NO_7S$: C, 66.04; H, 4.99; N, 2.57. Found: C, 65.56; H, 4.75; N, 2.59.

5-((4-Nitrophenyl)methyl)-2,3,8,9-tetramethoxy-6(5H)-phenanthridinone; m.p. 239-240°C. Anal. Calcd. for $C_{24}H_{22}N_2O_7$: C, 64.00; H, 4.92; N, 6.22. Found: C, 63.66; H, 4.71; N, 6.16.

5-((4-Methoxyphenyl)methyl-2,3,8,9-tetramethoxy-6(5H)-phenanthridinone; m.p. 199-200°C. Anal. Calcd. for $C_{25}H_{25}NO_6$: C, 70.58; H, 5.92; N, 3.29. Found: C, 68.16; H, 5.54; N, 3.17.

5-Ethyl-2,3,7,8-tetramethoxy-6(5H)-phenanthridinone; m.p. 139-141°C. Anal. Calcd. for $C_{19}H_{21}NO_5$: C, 66.47; H, 6.17; N, 4.08. Found: C, 66.13; H, 6.03; N, 3.98.

5-Phenylmethyl-2,3,7,8-tetramethoxy-6(5H)-phenanthridinone; m.p. 183-184°C (acetone/cyclohexane). Anal. Calcd. for $C_{24}H_{23}NO_5$: C, 71.10; H, 5.72; N, 3.46. Found: C, 70.86; H, 5.68; N, 3.40.

5-((4-Nitrophenyl)methyl)-2,3,7,8-tetramethoxy-6(5H)-phenanthridinone; m.p. 191-193°C. Anal. Calcd. for $C_{24}H_{22}N_2O_7$: C, 64.00; H, 4.92; N, 6.22. Found: C, 63.65; H, 4.65; N, 6.30.

5-((3,4-Dichlorophenyl)methyl)-2,3,7,8-tetramethoxy-6(5H)-phenanthridinone; m.p. 172-173°C. Anal. Calcd. for $C_{24}H_{21}Cl_2NO_5$: C, 60.78; H, 4.46; N, 2.95. Found: C, 60.66; H, 4.52; N, 2.92.

5-(((4-Phenylsulfonyl)phenyl)methyl)-2,3,7,8-tetramethoxy-6(5H)-phenanthridinone; m.p. 189-191°C.

Anal. Calcd. for $C_{30}H_{27}NO_7S$: C, 66.04; H, 4.99; N, 2.57. Found: C, 64.31; H, 4.70; N, 2.60.

5-((3-Phenyl)propyl)-2,3,8,9-tetramethoxy-6(5H)-phenanthridinone; m.p. 209-211°C (chloroform/MeOH). Anal. Calcd. for $C_{26}H_{27}NO_5$: C, 72.05; H, 6.28; N, 3.23. Found: C, 71.38; H, 6.03; N, 3.20.

PREPARATION 7

A

2,3,6,7-Tetramethoxy-fluoren-9-one - Ethyl 2-((3,4-dimethoxy)phenyl)-4,5-dimethoxybenzoate (2.25 g, 6.50 mmol) was added to a stirred mixture of concentrated sulfuric acid/water (93:7 v/v, 30 mL) producing a slightly exothermic reaction. The resulting green solution was stirred at ambient temperature for 1 hour. The reaction solution ws poured onto ice (70 g) and extracted with EtOAc. The organic phase was washed with saturated aqueous sodium bicarbonate, brine, dried (Na_2SO_4), filtered and concentrated in vacuo to afford orange solids. The solids were recrystallized from MeOH to provide the title compound as orange crystals (1.67 g); m.p. 200-202°C. Anal. Calcd. for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 67.50; H, 5.37.

The following compounds (B-D) were prepared from the appropriate starting material using the above general procedure:

1,2-Dimethoxyfluoren-9-one; m.p. 110-111°C (EtOAc/cyclohexane). Anal. Calcd. for $C_{15}H_{12}O_3$: C, 75.00; H, 5.04. Found: C, 74.88; H, 4.83.

2,3-Dimethoxyfluoren-9-one; m.p. 158-160°C.

1,2,6,7-Tetramethoxyfluoren-9-one; m.p. 208-209°C (dioxane/water). Anal. Calcd. for $C_{17}H_{17}O_5$: C, 67.99; H, 5.37. Found: C, 67.77; H, 5.19.

PREPARATION 8

A

N-9H-2,3,6,7-Tetramethoxyfluoren-9-ylidene-(4'-trifluoromethyl)benzamine - To an intimate mixture of 2,3,6,7-tetramethoxyfluoren-9-one (0.60 g, 2.00 mmol) and 4-(trifluoromethyl)benzylamine (0.97 g, 6.00 mmol) under nitrogen was added boron trifluoride etherate (0.2 mL). The resulting dark mixture was heated at 200°C for 1 hour, cooled and dissolved in a mixture of saturated aqueous sodium bicarbonate/EtOAc. The organic phase was washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The resulting solids were recrystallized from methanol to afford the title compound as yellow crystals (0.20 g); m.p. 207-209°C. Anal. Calcd. for $C_{24}H_{20}F_3NO_4$: C, 65.00; H, 4.55; N, 3.16. Found: C, 64.83; H, 4.25; N, 3.01.

The following compounds (B-H) were prepared from the appropriate starting material using the above general procedure:

N-9H-2,3,6,7-Tetramethoxyfluoren-9-ylidene-benzamine; m.p. 191-192°C. Anal. Calcd. for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64; N, 3.73. Found: C, 72.66; H, 5.56; N, 3.62.

N-9H-2,3,67-Tetramethoxyfluoren-9-ylidene-(4'-cyano)benzamine; m.p. 266-269°C. Anal. Calcd. for $C_{24}H_{20}N_2O_4$: C, 71.98; H, 5.03; N, 7.00. Found: C, 70.53; H, 4.71; N, 6.73.

N-9H-1-Hydroxy-2,6,7-trimethoxyfluoren-9-ylidene-benzamine; m.p. 175-176°C (MeOH). Anal. Calcd. for $C_{22}H_{19}NO_4$: C, 73.11; H, 5.30; N, 3.88. Found: C, 72.75; H, 4.92; N, 3.71.

N-9H-1-Hydroxy-2,6,7-trimethoxyfluoren-9-ylidene-(3,5-dichloro)benzamine; m.p. 201-203°C. Anal. Calcd. for $C_{22}H_{17}Cl_2NO_4$: C, 61.42; H, 3.98; N, 3.26. Found: C, 61.33; H, 3.92; N, 3.22.

N-9H-1-Hydroxy-2,6,7-trimethoxyfluoren-9-ylidene-(4'-nitro)benzamine; m.p. 211-215°C. Anal. Calcd. for $C_{22}H_{18}N_2O_6$: C, 65.02; H, 4.46; N, 6.89. Found: C, 64.70; H, 4.40; N, 6.64.

N-9H-1-Hydroxy-2,6,7-trimethoxyfluoren-9-ylidene-(4'-i-propyl)benzamine; m.p. 184-185°C (EtOAc/hexanes). Anal. Calcd. for $C_{25}H_{25}NO_4$: C, 74.43; H, 6.25; N, 3.47. Found: C, 74.36; H, 6.17; N, 3.49.

N-9H-1-Hydroxy-2,6,7-trimethoxyfluoren-9-ylidene-(4'-methylsulfonyl)benzamine; m.p. 203-205°C (acetone/hexanes). Anal. Calcd. for $C_{23}H_{21}NO_6S$: C, 62.86; H, 4.82; N, 3.19. Found: C, 62.37; H, 4.82; N, 3.22.

PREPARATION 9

A

2,3,6,7-Tetramethoxy-9H-fluorene - A slurry of 2,3,6,7,-tetramethoxy-fluoren-9-one (1.33 g, 4.43 mmol) and 10% palladium-on-carbon (0.4 g) was shaken on a Parr apparatus under 50 psi hydrogen pressure for 24 hours. Hot acetone (50 mL) was added and the reaction mixture was filtered through Celite, washing with several portions of hot acetone. The combined filtrates were concentrated in vacuo and the resulting solids were titrated with MeOH to afford the title

compound as gray solid (1.15 g); m.p. 193-195°C. Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.01; H, 6.32.

The following compounds (B-C) were prepared from the appropriate starting material using the above general procedure:

1,2-Dimethoxy-9H-fluorene; m.p. 99-101°C.

2,3-Dimethoxy-9H-fluorene; ^{1}H-NMR (d_6-DMSO) delta 7.78 (d, 1H), 7.52-7.46 (m, 2H), 7.31 (dd, 1H), 7.22 - 7.14 (m, 2H).

PREPARATION 10

1,2,6,7-Tetramethoxy-9H-fluorene - To a cooled (0°C), stirred slurry of 1,2,6,7-Tetramethoxy-fluoren-9-one (6.7 g, 22 mmol) in THF (45 mL) was added a 1M solution of lithium aluminum hydride (22 mL, 22 mmol) in THF over a 5 minute period. The resulting solution was stirred at room temperature for 1 hour, recooled to 0°C, quenched with water (4 mL) and 1N NaOH (0.6 mL). The resulting solids were filtered and washed with hot acetone. The combined filtrates were concentrated in vacuo to a yellow solid. These solids (8.6 g) were dissolved in a 1:1 mixture (200 mL) of THF and acetic acid, 10% palladium-on-carbon (8.6 g) was added and the resulting slurry was shaken on a Parr apparatur under 45 psi hydrogen pressure for 4 hours. The reaction mixture was filtered through Celite, washed with acetone and the combined filtrates were concentrated in vacuo. The resulting solids were recrystallized from acetone/hexane to afford the title compound (4.7 g); m.p. 170-172°C. Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 70.70; H, 6.37.

PREPARATION 11

A

9-(((4-Trifluoromethyl)phenyl)methylene)-2,3,6,7-tetramethoxyfluorene - To a cooled (0°C), stirred slurry of 2,3,6,7-tetramethoxy-9H-fluorene (0.50 g, 1.75 mmol) in pyridine (1.5 mL) was added Triton B (40% in MeOH, 0.05 mL) and a solution of 4-(trifluoromethyl)benzaldehyde (0.46 g, 2.62 mmol) in pyridine (1.5 mL). The reaction mixture was allowed to stir at room temperature for 36 hours, additional portions of 4-(trifluoromethyl)benzaldehyde (0.2 g, 0.9 mmol) and Triton B (0.05 mL) were added. The reaction mixture was heated at 60°C for 18 hours, cooled and diluted into EtOAc. This mixture was washed with water, brine, dried (Na_2SO_4), filtered and concentrated in vacuo. Flash chromatography (30% acetone/hexane) of the residue afforded the title compound (0.56 g) as an orange solid; m.p. 163-165°C. Anal. Calcd. for $C_{25}H_{21}F_3O_4$: C, 67.87; H, 4.79. Found: C, 67.55; H, 4.56.

The following compounds (B-H) were prepared from the appropriate starting material using the procedure detailed above:

9-(Phenylmethylene)-1,2-dimethoxyfluorene; m.p. 106-110°C.

9-((4-Quinolyl)methylene-1,2-dimethoxyfluorene; m.p. 210°C (acetone/cyclohexane). Anal. Calcd. for $C_{25}H_{19}NO_2$: C, 82.17; H, 5.24; N, 3.83. Found: C, 82.23; H, 5.00; N, 3.88.

9-(Phenylmethylene)-2,3,6,7-tetramethoxyfluorene; foam. ^{1}H-NMR (d_6-DMSO) delta 7.62 (s, 1H), 7.55 (d,

2H), 7.51-7.42 (m, 3H), 7.41-7.32 (m, 3H), 6.83 (s, 1H), 3.84 (s, 3H), 3.82 (s, 6H), 3.42 (s, 3H).

9-((4-Methoxyphenyl)methylene)-2,3,6,7-tetramethoxyfluorene; m.p. 179-180°C. Anal. Calcd. for $C_{25}H_{24}O_5$: C, 74.24; H, 5.98. Found: C, 73.95; H, 5.84.

9-((4-Quinolyl)methylene)-2,3,6,7-tetramethoxyfluorene; m.p. 226-228°C (acetone/cyclohexane). Anal. Calcd. for $C_{27}H_{23}NO_4$:

9-((4-Methoxyphenyl)methylene)-1,2,6,7-tetramethoxyfluorene; m.p. 138-140°C (EtOAc/hexanes). Anal. Calcd. for $C_{25}H_{24}O_5$: C, 74.24; H, 5.98. Found: C, 73.85; H, 5.88.

9-((4-Quinolyl)methylene)-1,2,6,7-tetramethoxyfluorene; m.p. 203-205°C (acetone/cyclohexane). Anal. Calcd. for $C_{27}H_{23}NO_4$: C, 76.23; H, 5.45; N, 3.29. Found: C, 75.66; H, 5.13; N, 3.24.

PREPARATION 12

A

9-((4-Methoxyphenyl)methyl)-2,3,6,7-tetramethoxyfluorene - A slurry of 9-((4-Methoxyphenyl)methylene)-2,3,6,7-tetramethoxyfluorene (0.35 g, 0.89 mmol) and 10% palladium-on-carbon (0.04 g) in THF (5 mL) were shaken in a Parr apparatus under 50 psi of hydrogen for 4 hours. The reaction mixture was filtered through Celite, washed with acetone and the filtrates were concentrated in vacuo. The residue was flash chromatographed (30% acetone/hexanes) to afford the title compound (0.33 g); m.p. 168-169°C (MeOH). Anal. Calcd. for $C_{25}H_{26}O_5$: C, 73.88; H, 6.45. Found: C, 73.89; H, 6.35.

The following compounds (B-G) were prepared from the appropriate starting material using the procedure described above:

9-(Phenylmethyl)-1,2-dimethoxyfluorene; m.p. 93-96°C. Anal. Calcd. for $C_{22}H_{20}O_2$: C, 83.36; H, 6.32.

9-(Phenylmethyl)-2,3,6,7-tetramethoxyfluorene; m.p. 143-144°C (EtOAc/hexanes). Anal. Calcd. for $C_{24}H_{24}O_4$: C, 76.58; H, 6.43. Found: C, 75.95; H, 6.35.

9-(Phenylmethyl)-1,2,6,7-tetramethoxyfluorene; foam. ^{1}H-NMR (d_6-DMSO) delta 7.36 (d, 1H), 7.27 (s, 1H), 7.20-7.07 (m, 3H), 7.06-6.97 (m, 3H), 6.49 (s, 1H), 4.28 (dd, 1H), 3.96 (s, 3H), 3.87 (s, 3H), 3.80 (s, 3H), 3.73 (dd, 1H), 3.58 (s, 3H), 2.80 (dd, 1H).

9-((4-Pyridyl)methyl)-2,3,6,7-tetramethoxyfluorene; m.p. 169-171°C (acetone/hexanes). Anal. Calcd. for $C_{23}H_{23}NO_4$: C, 73.20; H, 6.14; N, 3.71. Found: C, 72.81; H, 6.15; N, 3.67.

9-((4-Quinolyl)methyl)-1,2-dimethoxyfluorene; m.p. 114-116°C (EtOAc/hexanes). Anal. Calcd. for $C_{25}H_{21}NO_2$: C, 81.72; H, 5.76; N, 3.81. Found: C, 81.60; H, 5.55; N, 3.76.

9-((4-Quinolyl)methyl)-2,3,6,7-tetramethoxyfluorene; m.p. 176-179°C.

PREPARATION 13

A

1,2,6,7-Tetramethoxy-9H-carbazole/2,3,6,7-Tetramethoxy-9H-carbazole - A stirred solution of 2-((3,4-dimethoxy)phenyl)-4,5,-dimethoxynitrobenzene (6.5 g, 20 mmol) in triethylphosphite (10.5 mL, 6.11

mmol) was heated at 160°C under a nitrogen atmosphere for 10 hours. The excess triethylphosphite was removed in vacuo, residue was slurried in chloroform the solids were filtered and recrystallized from EtOAc to afford 2,3,6,7-tetramethoxy-9H-carbazole (1.9 g); m.p. 232-233°C. Anal. Calcd. for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.97; N, 4.88. Found: C, 65.04; H, 5.62; N, 4.71. The chloroform filtrate from above was concentrated in vacuo and flash chromatographed (20% EtOAc/CCl_4) to afford 1,2,6,7-tetramethoxy-9H-carbazole (1.7 g); m.p. 170-171°C (MeOH). Anal. Calcd. for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.97; N, 4.88. Found: C, 66.75; H, 5.80; N, 4.88.

The following compounds (B) were prepared from the appropriate starting material using the above general procedure:

2,3-Dimethoxy-9H-carbazole; m.p. 188-189°C.

PREPARATION 14

2-((2-Bromo-4,5-dimethoxy)phenyl)-4,5-dimethoxy-nitrobenzene - To a stirred solution of 2-((3,4-dimethoxy)phenyl)-4,5-dimethoxynitrobenzene (0.5 g, 1.6 mmol) and sodium acetate (0.3 g, 4.0 mmol) in nitromethane (6 mL) was added a solution of bromine (0.5 g, 3.1 mmol) in glacial acetic acid (0.5 mL). After 1 hour, the reaction solution was poured into saturated aqueous sodium bicarbonate and extracted with EtOAc. The organic layer was washed with water, brine, dried (Na_2SO_4), filtered and concentrated in vacuo to afford the title compound (0.6 g); m.p. 172-174°C. Anal. Calcd. for $C_{16}H_{16}BrNO_6$: C, 48.25; H, 4.05; N, 3.52. Found: C, 48.24; H, 3.93; N, 3.47.

PREPARATION 15

4-Bromo-1,2,6,7-tetramethoxy-9H-carbazole - A stirred solution of 2-((2-bromo-4,5-dimethoxy)phenyl)-4,5-dimethoxynitrobenzene (0.54 g, 1.37 mmol) in triethylphosphite was heated at 160°C for 10 hours. The excess triethylphosphite was removed in vacuo and the residue was recrystallized from EtOAc to afford the title compound (0.19 g); m.p. 206-207°C. Anal. Calcd. for $C_{16}H_{16}BrNO_4$: C, 52.47; H, 4.40; N, 3.83. Found: C, 53.07; H, 4.11; N, 3.93.

PREPARATION 16

A

9-(phenylmethyl)-2,3,6,7-tetramethoxycarbazole - To a stirred solution 2,3,6,7-tetramethoxy-9H-carbazole (0.6 g, 2.0 mmol) in anhydrous dimethylsulfoxide (5 mL) was added sodium hydride (60% in oil, 0.16 g, 4.0 mmol). After 0.5 hour, benzyl bromide (2.0 g, 12 mmol) was added, the reaction mixture was stirred for 1 hour, diluted into water and extracted into EtOAc. The organic layer was washed with water, brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was flash chromatographed (14% EtOAc/CCl_4) to afford the title compound (0.7 g); m.p. 174-176°C. Anal. Calcd for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71. Found: C, 73.06; H, 5.83; N, 3.66.

The following compounds (B-Z and AA-AH) were prepared from the appropriate starting material using the above general procedure:

9-Benzoyl-2,3-dimethoxycarbazole; m.p. 155-157°C.

9-Benzoyl-1,2,6,7-tetramethoxycarbazole; m.p. 184-185°C (MeOH). Anal. Calcd. for $C_{23}H_{21}NO_5$: C,

70.57; H, 5.41; N, 3.58. Found: C, 70.37; H, 5.25; N, 3.49.

9-Benzoyl-2,3,6,7-tetramethoxycarbazole; m.p. 181-182°C (MeOH). Anal. Calcd. for $C_{23}H_{21}NO_5$: C, 70.57; H, 5.41; N, 3.58. Found: C, 70.17; H, 5.35; N, 3.53.

9-(Phenylmethyl)-1,2,6,7-tetramethoxycarbazole; m.p. 174-175°C (MeOH). Anal. Calcd. for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71. Found: C, 73.06; H, 6.07; N, 3.66.

9-Methyl-2,3,6,7-tetramethoxycarbazole; m.p. 203-205°C. Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.62; H, 6.19; N, 4.52.

9-(Methylsulfonyl)-1,2,6,7-tetramethoxycarbazole; m.p. 164-165°C (MeOH). Anal. Calcd. for $C_{17}H_{19}NO_6S$: C, 55.88; H, 5.24; N, 3.83. Found: C, 55.40; H, 5.43; N, 3.49.

9-(Methylsulfonyl)-2,3,6,7-tetramethoxycarbazole; m.p. 207-210°C. Anal. Calcd. for $C_{17}H_{19}NO_6S$: C, 55.88; H, 5.24; N, 3.83. Found: C, 55.46; H, 5.11; N, 3.80.

9-(Phenylsulfonyl)-1,2,6,7-tetramethoxycarbazole; m.p. 205-206°C (MeOH). Anal. Calcd. for $C_{22}H_{21}NO_6S$: C, 61.81; H, 4.95; N, 3.28. Found: C, 61.87; H, 4.96; N, 3.11.

9-(Phenylsulfonyl)-2,3,6,7-tetramethoxycarbazole; m.p. 212-213°C (MeOH). Anal. Calcd. for $C_{22}H_{21}NO_6S$: C, 61.81; H, 4.95; N. 3.28. Found: C, 61.62; H, 4.79; N, 3.25.

9-(4-t-Butylbenzoyl)-1,2,6,7-tetramethoxy-carbazole; m.p. 129-131°C (MeOH). Anal. Calcd. for

$C_{27}H_{29}NO_5$: C, 72.46; H, 6.53; N, 3.13. Found: C, 72.28; H, 6.55; N, 3.11.

9-((4-Trifluoromethyl)benzoy)-1,2,6,7-tetramethoxycarbazole; m.p. 124-125°C (MeOH). Anal. Calcd. for $C_{24}H_{20}F_3NO_5$: C, 62.74; H, 4.39; N, 3.05. Found: C, 62.85;; H, 4.16; N, 2.95.

9-((4-Methylsulfonyl)benzoyl)-1,2,6,7-tetramethoxycarbazole; m.p. 171-172°C (MeOH). Anal. Calcd. for $C_{24}H_{23}NO_7S$: C, 61.39; H, 4.94; N, 2.98. Found: C, 61.58; H, 4.80; N, 2.90.

9-(4-Bromobenzoyl)-1,2,6,7-tetramethoxycarbazole; 157-158°C (MeOH). Anal. Calcd. for $C_{23}H_{20}BrNO_5.0.25H_2O$: C, 58.17; H, 4.35; N, 2.95. Found: C, 58.05; H, 4.23; N, 2.92.

9-(4-Phenylbenzoyl)-1,2,6,7-tetramethoxycarbazole: m.p. 150-153°C (MeOH). Anal. Calcd. for $C_{29}H_{25}NO_5$: C, 74.50; H, 5.39; N, 3.00. Found: C, 74.61; H, 5.07; N, 2.98.

9-(3-Phenylpropionyl)-1,2,6,7-tetramethoxycarbazole; m.p. 106-108°C (MeOH). Anal. Calcd. for $C_{25}H_{25}NO_5$: C, 71.58; H, 6.01; N, 3.34. Found: C, 71.57; H, 5.78; N, 3.23.

9-(2-Napthoyl)-1,2,6,7-tetramethoxycarbazole; m.p. 137-141°C (MeOH). Anal. Calcd for $C_{27}H_{23}NO_5$: C, 73.45; H, 5.25; N, 3.17. Found: C, 73.47; N, 4.89; N, 3.15.

9-(3-Nitrobenzoyl)-1,2,6,7-tetramethoxycarbazole; m.p. 187-191°C (MeOH). Anal. Calcd. for $C_{23}H_{20}N_2O_7$: C, 63.30; H, 4.62; N, 6.42. Found: C, 62.98; H, 4.39; N, 6.42.

9-(3-Pyridylmethyl)-2,3,6,7-tetramethoxycarbazole; m.p. 183-184°C. Anal. Calcd. for $C_{22}H_{22}N_2O_4$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.40; H, 5.74; N, 7.27.

9-((3-Methylphenyl)methyl)-1,2,6,7-tetramethoxycarbazole; m.p. 145-146°C. Anal. Calcd. for $C_{24}H_{25}NO_4$: C, 73.63; H, 6.44; N, 3.58. Found: C, 73.63; H, 6.28; N, 3.61.

9-((4-Cyanophenyl)methyl)-1,2,6,7-tetramethoxycarbazole; m.p. 147-148°C (MeOH). Anal. Calcd. for $C_{24}H_{22}N_2O_4$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.53; H, 5.43; N, 6.95.

9-((4-Trifluoromethylphenyl)methyl)-1,2,6,7-tetramethoxycarbazole; m.p. 145-146°C (MeOH). Anal. Calcd. for $C_{24}H_{22}F_3NO_4.0.5H_2O$: C, 63.42; H, 5.10; N, 3.08. Found: C, 63.73; H, 4.96; N, 3.12.

9-((2,6-Dichlorophenyl)methyl)-1,2,6,7-tetramethoxycarbazole; m.p. 207-210°C (CH_2Cl_2/MeOH). Anal. Calcd. for $C_{23}H_{21}Cl_2NO_4$: C, 61.89; H, 6.74; N, 3.14. Found: C, 61.58; H, 4.70; N, 3.12.

9-((4-Phenylsulfonyl)phenylmethyl)-1,2,6,7-tetramethoxycarbazole; m.p. 155-157°C (MeOH). Anal. Calcd. for $C_{29}H_{27}NO_6S$: C, 67.29; H, 5.26; N, 2.71. Found: C, 67.26; H, 5.07; N, 2.70.

9-(4-Bromophenylmethyl)-1,2,6,7-tetramethoxycarbazole; m.p. 143-144°C (CH_2Cl_2/MeOH). Anal. Calcd. for C, 60.53; H, 4.86; N, 3.07. Found: C, 60.55; H, 4.67; N, 2.98.

9-(3-Phenylpropyl)-1,2,6,7-tetramethoxycarbazole; m.p. 116-118°C (MeOH). Anal. Calcd. for

$C_{25}H_{27}NO_4.0.25H_2O$: C, 73.23; H, 6.76; N, 3.46. Found: C, 73.42; H, 6.71; N, 3.42.

9-((Phenylmethyl)sulfonyl)-1,2,6,7-tetramethoxycarbazole; m.p. 152-156°C.

9-((2,5-Dichlorophenyl)sulfonyl)-1,2,6,7-tetramethoxycarbazole; m.p. 221-224°C (CH_2Cl_2).

9-((4-Nitrophenyl)sulfonyl)-1,2,6,7-tetramethoxycarbazole; m.p. 188-189°C (MeOH). Anal. Calcd. for $C_{22}H_{20}N_2O_8S$: C, 55.92; H, 4.27; N, 5.93. Found: C, 55.91; H, 4.02; N, 5.84.

9-((4-Trifluoromethyl)benzoyl)-4-bromo-1,2,6,7-tetramethoxycarbazole; m.p. 167-168.5°C (MeOH). Anal. Calcd. for $C_{24}H_{19}BrF_3NO_5$: C, 53.54; H, 3.56; N, 2.60. Found: C, 53.63; H, 3.40; N, 2.57.

9-((4-Methylsulfonyl)benzoyl)-4-bromo-1,2,6,7-tetramethoxycarbazole; m.p. 227-229°C (MeOH). $C_{24}H_{22}BrNO_7S.0.5H_2O$: C, 51.71; H, 4.16; N, 2.55. Found: C, 51.98; H, 3.79; N, 2.46.

9-(4-t-Butylbenzoyl)-4-bromo-1,2,6,7-tetramethoxycarbazole; m.p. 136-138°C (MeOH). Anal. Calcd. for C, 61.60; H, 5.36; N, 2.66. Found: C, 62.12; H, 5.46; N, 2.61.

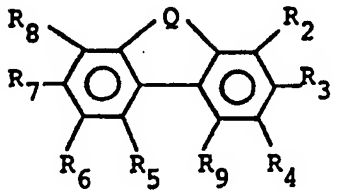
9-((4-Cyanophenyl)methyl)-4-bromo-1,2,6,7-tetramethoxycarbazole; m.p. 162-163°C. Anal. Calcd. for $C_{24}H_{21}BrN_2O_4$: C, 59.88; H, 4.40; N, 5.82. Found: C, 59.89; H, 4.21; N, 5.77.

9-(Methylsulfonyl)-4-bromo-1,2,6,7-tetramethoxycarbazole; m.p. 178-179°C (MeOH). Anal. Calcd. for $C_{17}H_{18}BrNO_6S$: C, 45.95; H, 4.08; N, 3.15. Found: C, 45.87; H, 3.99; N, 3.13.

It should be understood that the invention is not limited to the particular embodiments shown and described herein, but that various changes and modifications may be made without departing from the spirit and scope of this novel concept as defined by the following claims.

CLAIMS

1. A compound of formula I



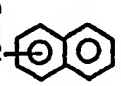
Formula I

wherein Q is $\diagdown N\text{-}Z_1$, $\diagdown C\text{-}Z_2$ or $-\overset{O}{\overset{\|}{C}}\text{-}X-$;

at least two and no more than four of R_2, R_3, R_4, R_5, R_6, R_7 and R_8 are OH, the remainder being H;

R_9 is H or halo, with the proviso that R_9 is halo only when Q is $\diagdown N\text{-}Z_1$;

Z_1 is H, benzyl, alkyl(C_1-C_4), $-(CH_2)_n$-phenyl-R_{22}, $-(CH_2)_n$-dichlorophenyl, $-\overset{O}{\overset{\|}{C}}-(CH_2)_n$-phenyl-$R_{20}$, $-SO_2-R_{21}$, $-CH_2$-pyridyl or



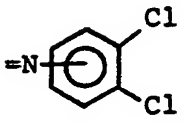
wherein n is 0-3;

R_{20} is H, t-butyl, CF_3, $-SO_2$-alkyl(C_1-C_4), halo, alkyl(C_1-C_4), phenyl or NO_2;

R_{21} is phenyl, alkyl(C_1-C_4), benzyl, nitrophenyl, dichlorophenyl or halophenyl;

R_{22} is $-C\equiv N$, CF_3, phenylsulfonyl, halo or alkyl(C_1-C_4);

Z_2 is H, =O, benzyl, hydroxylbenzyl, $=N$-phenyl-R_{10} $=CH$-phenyl-R_{10}, $-CH_2$-pyridyl, $-CH_2$-quinolyl, $=CH_2$-pyridyl, =CH-quinolyl or



wherein R_{10} is -C≡N, H, CF_3, OH, NO_2, alkyl(C_1-C_4) or -SO_2-alkyl(C_1-C_4) with the proviso that when Z_2 is bonded with a single bond to the carbon to which it is attached, that that carbon is also bonded to a hydrogen;

X is N-Z_3 or O;

Z_3 is H, alkyl(C_1-C_4), -CH_2phenyl-R_{11} or (dichlorophenyl)methyl wherein R_{11} is H, -NO_2, -SO_2-  , hydroxyl or halo; and

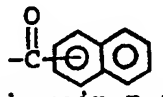
the pharmaceutically-acceptable cationic salts and prodrugs thereof.

2. A compound as recited in claim 1 wherein R_2, R_3 and R_4 are H or OH; R_6 and R_7 are OH; R_5 and R_8 are H; R_9 is H or halo;

Q is 

Z_1 is H, benzyl, alkyl(C_1-C_4), -$(CH_2)_n$-phenyl-R_{22}, -$(CH_2)_n$-dichlorophenyl,

 , -SO_2-R_{21}, -CH_2-pyridyl, and

 ;

wherein n is 0-3;

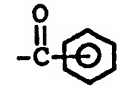
R_{20} is H, t-butyl, CF_3, -SO_2-alkyl(C_1-C_4), halo, alkyl(C_1-C_4), phenyl or NO_2;

R_{21} is phenyl, alkyl(C_1-C_4), benzyl, nitrophenyl, dichlorophenyl or halophenyl; and

R_{22} is -C≡N, CF_3, phenylsulfonyl, halo or alkyl(C_1-C_4).

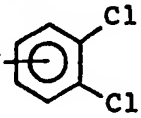
3. A compound as recited in claim 2 wherein R_2, R_3, R_6 and R_7 are OH; R_5 and R_8 are H; and R_9 is H or halo.

4. A compound as recited in claim 2 wherein R_3, R_4, R_6, R_7 are OH; R_2, R_5, R_8 and R_9 are H; and Z_1 is H, -C(=O)-phenyl, benzyl, -alkyl(C_1-C_4), -SO_2-phenyl, -SO_2-alkyl(C_1-C_4) and -CH_2-3-pyridyl.

5. A compound as recited in claim 2 wherein R_2, R_3, R_4, R_5, R_8 and R_9 are H; R_6 and R_7 are OH; and Z_1 is H or -C(=O)-  .

6. A compound as recited in claim 1 wherein

Q is  ;

Z_2 is H, =O, benzyl, hydroxybenzyl, =N-phenyl-R_{10}, =CH-phenyl-R_{10}, -CH_2-pyridyl, -CH_2-quinolyl, =CH_2-pyridyl, =CH-quinolyl or  ; and

R_{10} is -C≡N, H, CF_3, OH, NO_2, alkyl(C_1-C_4) and -SO_2-alkyl(C_1-C_4).

7. A compound of claim 6 wherein R_3, R_4, R_6 and R_7 are OH and R_2, R_5, R_8 are H.

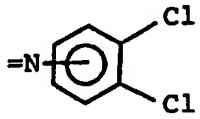
8. A compound of claim 7 wherein Z_2 is =N-phenyl-R_{10}; and R_{10} is H, -C≡N or CF_3.

9. A compound of claim 7 wherein Z_2 is =CH-phenyl-R_{10}; and R_{10} is H, OH or CF_3.

10. A compound of claim 7 wherein Z_2 is H, =O, benzyl, (4-hydroxyphenyl)methyl, -CH_2-4-pyridyl, -CH_2-4-quinolyl or =CH-4-quinolyl.

11. A compound of claim 6 wherein R_3, R_4, R_7 and R_8 are OH and R_2, R_5 and R_6 are H.

12. A compound of claim 11 wherein Z_2 is



or =N-phenyl-R_{10}; and R_{10} is H, NO_2, -C-$(CH_3)_2$ or -SO_2-CH_3.

13. A compound as recited in claim 11 wherein Z_2 is =O, benzyl, =CH-4-quinolyl or =CH-4-hydroxybenzyl.

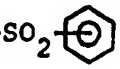
14. A compound of claim 6 wherein Z_2 is H or =O; R_6 and R_7 are OH; and R_2, R_3, R_4, R_5 and R_8 are H.

15. A compound of claim 6 wherein Z_2 is =O, benzyl, H, -CH_2-4-pyridyl, -CH_2-4-quinolyl, =CH-4-pyridyl, =CH-4-quinolyl or =CH-phenyl; R_7 and R_8 are OH; and R_2, R_3, R_4, R_5 and R_6 are H.

16. A compound as recited in claim 1 wherein Q is

Z_3 is H, alkyl(C_1-C_4), -CH_2-phenyl-R_{11} or (dichlorophenyl)methyl; and

R_{11} is H, -NO_2,



, hydroxyl or halo.

17. A compound as recited in claim 16 wherein X is -O-; and R_5 is H.

18. A compound as recited in claim 16 wherein X is N-Z_3; R_3, R_4, R_6 and R_7 are OH; and R_2, R_5 and R_8 are H.

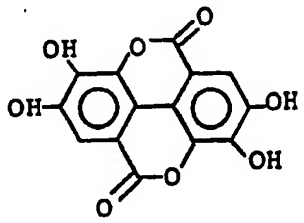
19. A compound as recited in claim 16 wherein X is N-Z_3; R_3, R_4, R_7 and R_8 are OH; and R_2, R_5 and R_6 are H.

20. A compound of claim 16 wherein X is N-Z_3; Z_3 and R_5 are H; and any two of R_2, R_3, R_4, R_6, R_7 and R_8 are OH.

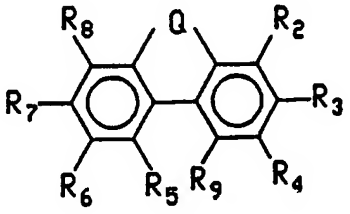
21. A pharmaceutical composition for the control of tyrosine kinase dependent diseases in mammals which comprises a compound of claim 1 in a pharmaceutically-acceptable carrier.

22. A method of controlling tyrosine kinase dependent diseases which comprises administering to a mammal suffering from a tyrosine kinase dependent disease a tyrosine kinase dependent disease controlling amount of a compound of claim 1.

23. A method of controlling tyrosine kinase dependent diseases which comprises administering to a mammal suffering from a tyrosine kinase dependent disease a tyrosine kinase dependent disease controlling amount of ellagic acid, the compound of the formula



24. A process for the preparation of a compound of Formula I

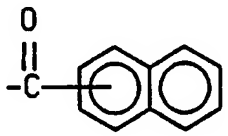


Formula I

wherein Q is $>N-Z_1$, $>C-Z_2$ or $-C(=O)-X-$;

at least two and no more than four of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 are OH, the remainder being H; R_9 is H or halo, with the proviso that R_9 is halo only when Q is $>N-Z_1$;

Z_1 is H, benzyl, alkyl(C_1-C_4), $-(CH_2)_n$-phenyl-R_{22}, $-(CH_2)_n$-dichloro-phenyl, $-C(=O)-(CH_2)_n$-phenyl-R_{20}, $-SO_2-R_{21}$, $-CH_2$-pyridyl or



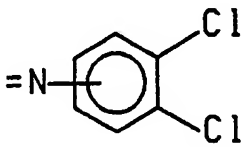
wherein n is 0-3;

R_{20} is H, t-butyl, CF_3, $-SO_2$-alkyl(C_1-C_4), halo, alkyl (C_1-C_4), phenyl or NO_2;

R_{21} is phenyl, alkyl(C_1-C_4), benzyl, nitrophenyl, dichlorophenyl or halophenyl;

R_{22} is -C=N, CF_3, phenylsulfonyl, halo or alkyl(C_1-C_4);

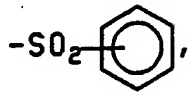
Z_2 is H, =O, benzyl, hydroxylbenzyl, =N-phenyl-R_{10}, =CH-phenyl-R_{10}, $-CH_2$-pyridyl, $-CH_2$-quinolyl, $=CH_2$-pyridyl, =CH-quinolyl or



wherein R_{10} is -C=N, H, CF_3, OH, NO_2, alkyl(C_1-C_4) or $-SO_2$-alkyl(C_1-C_4) with the proviso that when Z_2 is bonded with a single bond to the carbon to which it is attached, that that carbon is also bonded to a hydrogen;

X is N-Z_3 or O; and

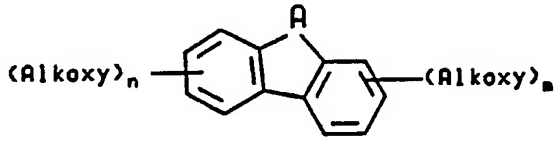
Z_3 is H, alkyl(C_1-C_4), $-CH_2$-phenyl-R_{11} or (dichlorophenyl)methyl wherein R_{11} is H, $-NO_2$,



, hydroxyl or halo comprising:

deprotecting a compound of the Formula XXV

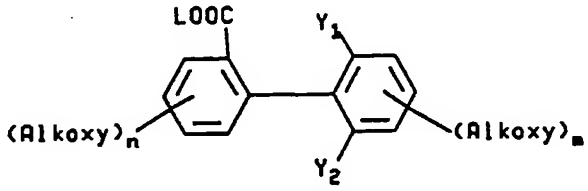
XXV



wherein A is  or -C(=O)-N(-Z_3)- as defined above; R_9 is as defined above; n plus m is at least two and no more than four; and alkoxy is C_1-C_4; or

deprotecting-cyclizing a compound of the Formula X

X



wherein n plus m is at least two and no more than four; O-L is a leaving group; and either Y_1 or Y_2 is alkoxy.

25. The process as recited in claim 24 wherein the deprotection/deprotecting-cyclizing is performed in a chlorinated solvent in the presence of a dealkylating agent at a temperature of about 0°C to about 80°C for about 1 hour to about 24 hours at pressures of about 0.1 psi to about 50 psi.

26. The process as recited in claim 25 wherein about 2 to about 5 equivalents of boron tribromide is used as the dealkylating agent and the process is performed at ambient temperature and pressure for 2 to 24 hours.

27. The process as recited in claim 24 wherein the deprotection/deprotecting-cyclizing is performed in HBr at a temperature of about 50°C to 100°C at about 0.1 psi to about 50 psi for about 1 hour to about 24 hours.

28. The process as recited in claim 26 wherein the Formula I compound prepared is 9-((4-cyanophenyl)methyl)-1,2,6,7-tetrahydroxycarbazole.

INTERNATIONAL SEARCH REPORT

International Applica No PCT/US 92/02799

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 221/12 C 07 D 209/88 C 07 D 311/80
A 61 K 31/435 A 61 K 31/40 A 61 K 31/465 C 07 C 39/17 C 07 C 49/747
C 07 C 39/23 C 07 D 213/30 C 07 D 215/14 C 07 C 252/20 C 07 C 255/61

II. FIELDS SEARCHED C 07 D 401/06

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 C C 07 D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	GB,A, 341905 (ARTHUR CARPMAEL) 14 January 1931, see example 1 ---	1-5
X	US,A,3932424 (W.L. ALBRECHT) 13 January 1976, see example 1 ---	1-5
X	Journal of the Chemical Society, part I, 1954, (London, GB), A. BARKER et al.: "3 : 6-Disubstituted fluorenes. Part II. The preparation of 3 : 6-diaminofluorene from fluorene, and the attempted internuclear cyclisation of derivatives of 4:4'-diaminodiphenylmethane", pages 870-873 --- -/-	1,6-15

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
20-08-1992	22.09.92
International Searching Authority	Signature of Authorized Officer
EUROPEAN PATENT OFFICE	Natalie Wallberg

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	Journal of Organic Chemistry, vol. 26, no. 11, November 1961, (Washington, DC, US), R.A. BARNES et al.: "Syntheses related to etiojervane. II. Synthesis of some substituted fluorenes", pages 4544-4548 ---	1,6-15
X	Liebigs Annalen der Chemie, vol. 5, 1973, (Weinheim, DE), L. HORNER et al.: "Versuche zur Darstellung von Chinonen des Fluorens und des Fluorenons", pages 910-935, see pages 910-935 ---	1,6-15
X	Patent Abstracts of Japan, vol. 5, no. 195 (C-083), 11 December 1981, & JP,A,56118069 (KANEOKA YUICHI) 16 September 1981, see abstract ---	1,16,18 -20
X	Chemical Abstracts, vol. 115, no. 25, 23 December 1991, (Columbus, Ohio, US), see page 993, abstract no. 279813d, & JP,A,02304080 (TOYO PHARMAR CO., LTD et al.) 17 December 1990 ---	1,16,17
X	Journal of the Chemical Society, Perkin Transaction I, 1981, (London, GB), F.R. VAN HEERDEN et al.: "Metabolites from the purple heartwoods of the mimosoideae. Part 4. Acacia fasciculifera F. Muell ex. Benth: fasciculiferin, fasciculiferol, and the synthesis of 7-aryl- and 7-flavanyl-peltogynoids", pages 2483-2490, see page 2483, compound 6 ---	1,16,17
X	Chemical Abstracts, vol. 114, no. 3, 21 January 1991, (Columbus, Ohio, US), J.P. DAVID et al.: "Inhibition of benzo[a]pyrene dihydrodiol epoxide mutagenicity by synthetic analogs of ellagic acid", see page 244, abstract no. 19258j, & MUTAT. RES. 1990, 242(2), 143-9, see abstract ---	1,16,17
X	Chemical Abstracts, vol. 93, no. 23, 8 December 1980, (Columbus, Ohio, US), B. DOYLE et al.: "The metabolism of ellagic acid in the rat", see page 9, abstract no. 215211a, & XENOBIOTICA 1980, 10(4), 247-56, see abstract -----	1,16,12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 92/ 02799

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 22-23: Method of treatment of the human body by therapy (Rule 39.1 (iv))Against a reformulated claim 23 to a searchable one, may arise, an objection against unity, the compound "ellugic acid" being a known product not covered by any claims 1-21 .

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9202799 SA 60179

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 16/09/92 The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A- 341905		None	
US-A- 3932424	13-01-76	None	

EPO FORM P0479

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82